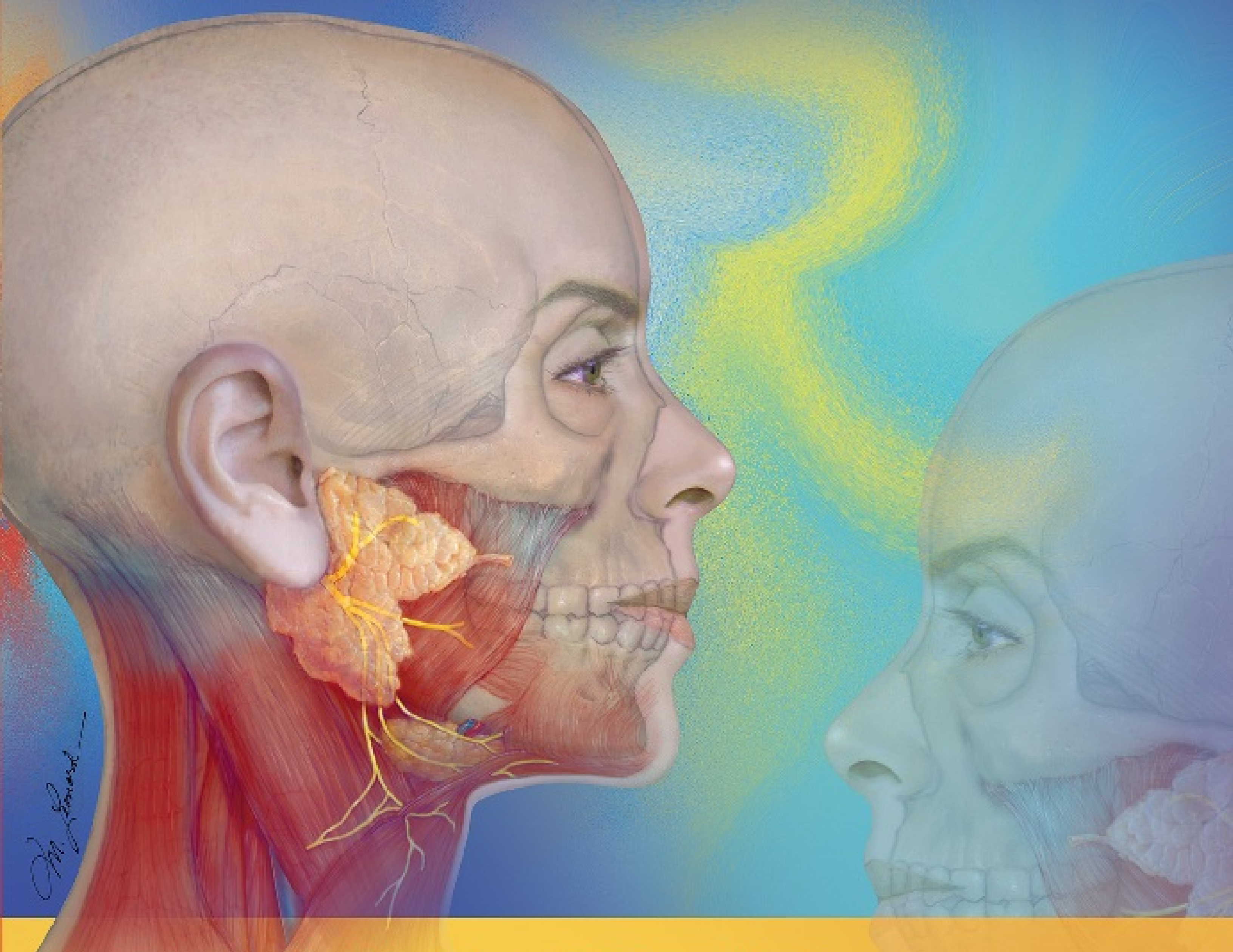

CANCER
of the Head and Neck

5th EDITION

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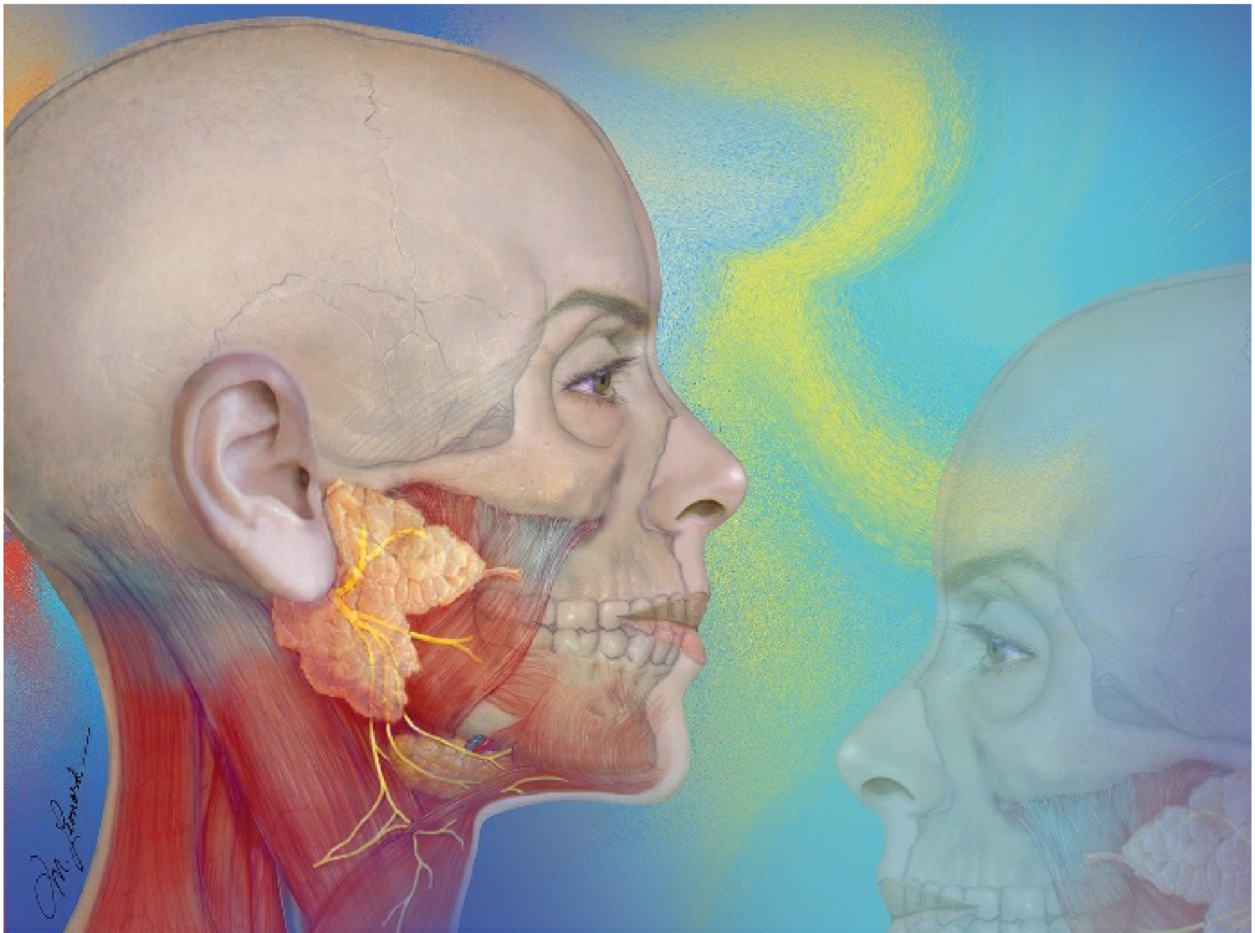

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Cancer of the Head and Neck

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This book is dedicated to my wife, Lisa, and our children, Keith Nicholas Myers, Brett Alexander Myers, and Blake David Myers, and to my parents, Eugene and Barbara Myers.

—JNM

This book is dedicated to my wife, Sylvie, for her grace, sacrifice, and support throughout my career; our daughters, Gabrielle Grace (Gigi) Hanna and Camille Lauren Hanna, for the joy and blessing they bring to our lives; my parents who encouraged me to follow my dreams; my mentors who inspired me to pursue excellence; my residents and students who continue to teach me; and my patients whose endurance, resilience, and faith continue to amaze me.

—EYH

This book is dedicated to my wife and best pal, Barbara; our son, Jeffrey N. Myers, MD, PhD, his wife, Lisa, and their sons, Keith N. Myers, Brett A. Myers, and Blake D. Myers; our daughter, Marjorie M. Fulbright, her husband, Cary, and their sons, Alexander F. Fulbright and Charles J. Fulbright, who are a constant source of joy and inspiration; to my parents, the late Dr. David and Rosalind N. Myers, whose dedication to patient care was a way of life; to the late Dr. John Conley with whom I learned the

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—ENM

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PREFACE

The management of cancer of the head and neck requires the efforts of a well-integrated multidisciplinary team for patients to achieve their highest oncologic outcomes and functional potential. Critically important team members include extirpative and reconstructive surgeons, radiation and medical oncologists, specialized radiologists and pathologists, as well as oral and maxillofacial surgeons and prosthodontists, speech pathologists, nutritionists, social workers, physical therapists, medical specialists, and anesthesiologists and pain management providers. In different practice settings, the team members may or may not necessarily work in the same office, clinic, or inpatient unit, and therefore, excellent communication, leadership, and agreement of all team members that the patient's well-being is the highest priority are needed for the team to be maximally successful. The head and neck surgeon often assumes the role of team leader as most head and neck cancer patients are initially referred to a head and neck surgeon. However, as the concept of nonsurgical organ preservation has become widely practiced in our field, it appears that chemotherapy and radiation therapy have become the first line of treatment for many patients with upper aerodigestive tract squamous cancers, necessitating that nonsurgical oncologists share the leadership role in coordinating multidisciplinary oncologic and rehabilitative care.

Cancer of the Head and Neck was written primarily for surgeons in its earlier editions, and while this edition maintains a surgical focus, it provides a comprehensive multidisciplinary approach to the entire head and neck cancer care team. In this fifth edition, we have incorporated disease- and site-specific chapters and have also given more emphasis to reconstruction and rehabilitation of the patient. The major change has not been so much in new chapters as in new authors, and we have searched for colleagues both in the United States and abroad to contribute to the book to make it contemporary and not to overlook any item that would contribute to the understanding and

management of this disease. The book remains faithful in this edition to its original intent, which is to provide a practical guide to practitioners, trainees, and allied health professionals caring for patients with head and neck cancer while maintaining a scholarly, contemporary, and comprehensive coverage of the complexity of head and neck oncology.

We hope that you will find this book helpful as you care for your patients.

Jeffrey N. Myers
Ehab Y. N. Hanna
Eugene N. Myers

CONTENTS

1 Perspectives in Cancer of the Head and Neck

Eugene N. Myers

PERSPECTIVES IN HEAD AND NECK CANCER

In the years which have passed since the 4th Edition of Cancer of the Head and Neck, many changes have taken place in the management of benign and malignant tumors of the head and neck. When my career as a head and neck surgeon began 46 years ago, most cancers of the head and neck were treated surgically using an external approach. Halsted’s concept of en bloc resection to be certain that the cancer was adequately removed often left the patient with cancer of the head and neck a functional cripple and a dreadful sight to behold. The only flaps available were delayed from a distant site such as the abdomen or the back. This form of reconstruction took many months, and by the time the patient’s reconstruction had been completed, often the cancer had recurred. The patient who underwent a total laryngectomy had little chance of ever speaking again and became a social outcast.

Radiation therapy was used with curative intent to treat early cancers of the tonsil and larynx or those deemed unresectable. Salvage surgery for those who failed radiation was fraught with danger due to the high doses used and because little attention was given to the fact that these patients were nutritionally depleted. This set of circumstances led to poor wound healing, necrosis of skin flaps, carotid artery blowout, and death. Even those who survived had great difficulties swallowing and often spent their remaining time on earth being nourished through a gastrostomy tube.

Chemotherapy was in the early developmental phase and used exclusively in the setting of massive local regional recurrence or distant

metastasis. Thus, each of the major modalities used to treat head and neck cancer today was quite primitive in comparison to today's state-of-the-art treatments.

A major advance in head and neck surgery occurred in 1965, when Dr. Bakamjian[1] introduced the deltopectoral flap. I performed many of these flaps during my fellowship with Dr. John Conley in 1967. This was a game changer since it was the first regional flap that could be used nondelayed in the reconstruction of the head and neck. The fact that even the largest wound could be reliably reconstructed immediately pushed the envelope so the surgeons could take on more advanced cancers and create more radical operations. This flap was largely replaced when the pectoralis major myocutaneous flap was introduced by Dr. Steven Ariyan in 1979.[2] This flap could also be used without delay, and creative surgeons have found many uses for this flap, which is widely used even today.

Cranial facial surgery for skull base tumors was first described by Dr. Alfred Ketcham[3] at the NIH in 1963, and this technique still plays an important role in the management of these tumors despite the introduction of endonasal endoscopic skull base surgery.

During my career, I have witnessed the introduction of many new techniques including transoral CO_2 laser microsurgery for vocal cord cancers by Strong and Jako[4] and the use of this technology by Steiner[5] in the excision of cancers of the supraglottis and hypopharynx. Weinstein et al.[6] later adapted the surgical robot (da Vinci) to successfully remove cancers of the oropharynx. The use of these techniques has preserved the historic role of the surgeon as a key individual in the management of cancer of the head and neck.

For those unfortunate patients who require total laryngectomy, the introduction of microvascular free tissue transfer has played a major role in reconstruction of these wounds particularly in the setting of postradiation salvage surgery. Singer and Blom[7] made a huge contribution to the quality of life of these patients when they introduced the valve that uses pulmonary-driven air to allow the patient to speak by occluding the stoma—a powerful contribution, beautiful in its simplicity.

The importance of the surgical robot was grasped by many head and neck surgeons who recognized the versatility and precision built into this machine.

O'Malley and Weinstein[8] developed the transoral robotic surgery (TORS) technique, which has provided a corridor to resect cancers of the base of the tongue thereby eliminating the need for the classic external approaches such as the transhyoid or transmandibular approach of yesteryear. With the current epidemic of HPV-related squamous cell carcinoma in a younger, healthier, nonsmoking population, the TORS approach fills the need for complete cancer resection with clear margins with preservation of swallowing function. The swallowing function was often compromised after larger external techniques were used as well as with patients who in recent years had been treated with nonsurgical means by chemoradiation. When it was recognized that these cancers were more curable in this subset of patients, Genden et al.[9] recognized the advantage of "dose de-escalation," which included primary TORS surgery and when necessary postoperative radiation therapy in lower doses that preserved swallowing function eliminating the patient's long-term dependence on PEG tubes.

Management of the neck remains the keystone in the management of cancer of the head and neck. Prof. Gordon Snow from Amsterdam,[10] in his lecture to the American Society of Head and Neck Surgery in 1979, introduced the concept of extracapsular spread (ECS) of cancer in cervical lymph nodes and the poor prognosis it portended. This concept captured my imagination, and in our department, we studied more than 500 radical neck dissections from patients with squamous cell carcinoma of various sites and validated Snow's findings. Because of the poor prognosis with ECS, we introduced the use of postoperative chemoradiation with a significant improvement in survivorship.[11] Level I evidence for this approach was subsequently provided by Cooper and colleagues in the North America and Bernier and colleagues in Europe.[12]

The teaching of Dr. Hayes Martin,[13] Chief of the Head and Neck Service at Memorial Hospital, was that the use of any technique less than a radical neck dissection and then only when metastatic lymph nodes were present was irrational and he stated, "In my opinion, it is no more logical or tenable to propose any form of partial neck dissection in the treatment of cancer than it is to advocate a partial axillary or partial groin dissection." This concept was challenged by Bocca[14] in 1984 when he published a series of 843 cases of functional neck dissection, which preserved such vital structures as the spinal accessory nerve and jugular vein. The selective neck dissection, which

preserves all of the nonlymphatic structures and can be used in both N_0 and N_+ necks, has gained popularity in recent decades. This technique can also be used in the postchemoradiation setting and even be limited to one level, a concept introduced by Robbins[15] in his Rad Plat treatment program.

Koh,[16] in Korea, has introduced the use of a surgical robot to do neck dissections. This can now be done using a rhytidectomy approach, which leaves a barely perceptible scar. Chung,[17] in Korea, has also done several thousand thyroidectomies using the surgical robot.

One of the factors that has made our field so dynamic is the collaboration of our surgeons with industry in devising technological advances to solve what have been surgical dilemmas. This collaboration has led to improved quality of life for our patients. A few examples in addition to the surgical robot include endoscopic-assisted thyroidectomy, endonasal endoscopic skull base surgery, and transoral laser excision of oropharyngeal lesions.

The formation of teams to manage cancer of the head and neck has led to fundamental improvements in both the oncologic outcome and the patients' improved quality of life. The incorporation of radiation oncologists, medical oncologists, speech–language pathologists, maxillofacial prosthodontists, plastic and oromaxillofacial surgeons, head and neck nurses, and nutritionists has vastly improved the overall care of the patient with cancer of the head and neck. The concept of forming major centers for the resource-intensive care of these patients also results in improved cure rates. Dr. Amy Chen[18] pointed out that hospitals where large volumes of surgery were done achieved higher cure rates than did small-volume hospitals.

Of course, none of the above would have been possible without the tremendous improvement in training specialists in this field. Credit should be given to pioneer surgeons such as Hayes Martin, Alando Ballantine, Richard Jesse, Joseph Ogura, George Sisson, John Conley, and Hugh Biller. All of these individuals were leaders of either Residency Training Programs or Fellowship Programs or both. They taught their trainees, many of whom stayed in academic programs, and subsequently passed on their knowledge and experience to their own trainees. In 1977, the Joint Council for Advanced Training in Head and Neck Oncologic Surgery was formed through the collaborative efforts of the American Society for Head and Neck Surgery and the Society of Head and Neck Surgeons. This was chaired by Dr. John Lore,

Jr., and was comprised of otolaryngologists, surgical oncologists, and plastic surgeons who collaborated in the organization of a formal Head and Neck Fellowship Training Program. This program has undergone an evolution over the years, and now, most of these programs offer a one-year Clinical Fellowship in Head and Neck Surgery while others with the appropriate resources and support for scientific research offer programs of two or more years, which include surgical training and a meaningful experience in scientific research. The programs are carefully monitored through periodic site visits and a rigorous accreditation program. This ensures a high-quality group of 35 accredited programs producing well-trained head and neck surgeons who have become the leaders in our specialty.

The role of research in our field cannot be overemphasized. In otolaryngology, where most of the head and neck surgical specialists originate, all residents must have an exposure to research and are assigned a block of time with a faculty research mentor.

A group of head and neck surgical scientists has emerged in our specialty including Jeffrey N. Myers, Robert Ferris, Joseph Califano, James Rocco, and Wendell Yarborough. These individuals are all accomplished head and neck surgeons and are also NIH-funded research scientists. These individuals serve as role models for trainees in our field who aspire to eradicating cancer through scientific research. A remarkable stimulus to scientific research in our field is the Specialized Programs of Research Excellence (SPORE) grant program sponsored by the NIH. Recipients of these grants include the University of Pittsburgh, MD Anderson Cancer Center, University of Michigan, Johns Hopkins University, and Emory University. Through the study of the biologic and genetic bases of cancer development, progression, and response to treatment, we should be able to identify more effective and less toxic means to prevent and treat these deadly cancers that we deal with on a daily basis. Developing precision treatment of these tumors will enable molecular targeting of drugs for specific tumors. This is exemplified by the use of cetuximab, which followed the discovery of EGFR and the demonstration of its importance in squamous cell carcinoma of the head and neck tumor progression.

I didn't begin my career in medicine wanting to be a head and neck surgeon because little was known about it and it seemed sort of primitive, but I'm proud to have spent my career as a head and neck surgeon, saving a

myriad of lives using cold steel and training a myriad of residents and fellows to do the same. I'm extremely proud of the progress made in our specialty, and I have no doubt that this cadre of remarkable surgical scientists will be leaders of our field and that they will continue to strive for prevention using basic science discoveries while taking care of those already afflicted with this meanspirited disease.

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2 Pathogenesis and Progression of Squamous Cell Carcinoma of the Head and Neck

Ryan M. Aronberg, Natalia Issaeva and Wendell G. Yarbrough

Over the past few decades, advances in cellular and molecular biology have led to an accelerated understanding of the pathogenesis and hallmarks of neoplastic disease. More recently, the development of array technologies and high-throughput genetic sequencing have helped to identify many of the underlying molecular defects involved in carcinogenesis and resistance to therapeutics. These capabilities have led to an overwhelming volume of data, requiring advances in bioinformatics to keep pace. The wealth of information being produced has laid the foundation to develop new treatments targeting these defects. Future goals will be the identification of biomarkers to guide diagnosis and therapy, the development of new targeted and combined therapies, and the personalization of therapy based on the molecular characteristics of individual tumors. It will become ever more important for clinicians to understand the molecular characteristics of the disease in caring for their patients. Overall, recent advances in the understanding of tumor biology and related fields (e.g., immunology) make this an exciting time of discovery that should translate into increased survival and improved quality of life for our patients.

This chapter will provide a framework to be used as a basis for exploring the pathogenesis of neoplasia, with an emphasis on the latest findings in head and neck squamous cell carcinoma (HNSCC). We will first introduce general concepts of carcinogenesis and then review the characteristics of the neoplastic phenotype and genotype seen in HNSCC. Along the way, recent biologic insight and therapeutic applications for HNSCC will be explored.

THEORIES OF CARCINOGENESIS

Clonal Evolution and Molecular Progression Models

It is widely accepted that an accumulation of alterations in several genes ultimately leads to a transition from normal to dysplastic to a neoplastic phenotype. Clonal evolution theory, proposed by Peter Nowell in 1976, likens cancer to an evolutionary process involving clonal proliferation, genetic diversification, and subclonal selection.[1] Random mutational events, in conjunction with selective pressures within the tumor environment (tissue barriers, the immune system, induction of programmed cell death, anticancer therapeutics), allow genetic diversification and drift. The cumulative loss of tumor suppressor genes or activation of oncogenes leads to changes in cellular behavior, which confers a survival or proliferative advantage over other cells, ultimately resulting in territorial expansion.[2] Eventually, the further accumulation of defects can confer new traits such as immortality, angiogenesis, or the ability to invade.

Colon cancer represents the first and most comprehensive molecular progression model.[3] In the model, events including oncogene activation and tumor suppressor inactivation lead to progression from normal mucosa, to benign adenomatous growth, to carcinoma in situ, to invasive carcinoma. As in colon cancer, it is the accumulation of these events, rather than an ordered occurrence, that leads to HNSCC,[4] and a similar histologic progression occurs from normal mucosa, to dysplastic mucosa, to carcinoma in situ, to frank invasive carcinoma.

Field Cancerization

For decades, it has been observed that the “normal” mucosa adjacent to head and neck cancers has histologic and genetic alterations not unlike the cancer itself. Additionally, it is not uncommon for satellite lesions or second primaries to occur in HNSCC. These observations led to the “field cancerization” hypothesis that an entire field of mucosa, which is exposed to the same environmental factors, is at risk for carcinogenesis (Fig. 2.1).[5] This theory proposes that although a cancer develops from a small localized segment of the mucosal field, the surrounding cells within a larger field of

mucosa exist on a dysplastic spectrum and share some genetic alterations with the cancer. Early on, lesions can appear clinically and histologically normal, but molecular signatures can help identify altered cells at risk for progression to cancer.

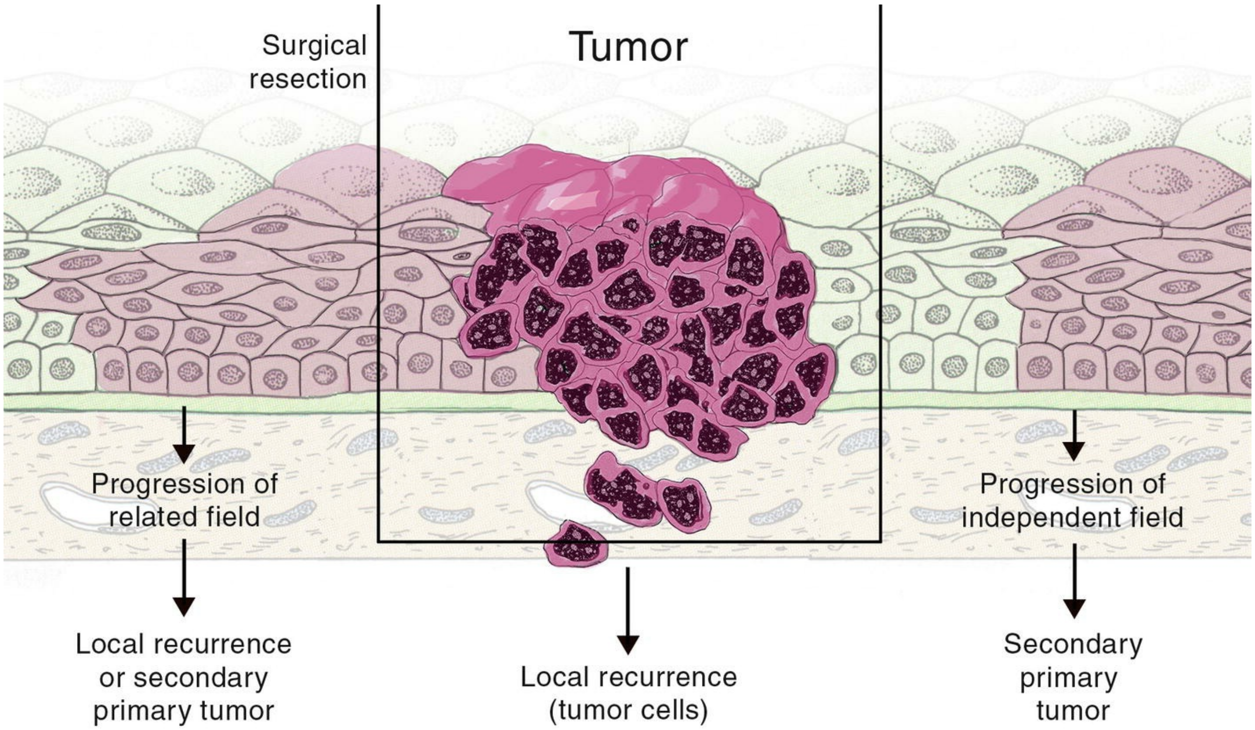


Figure 2.1. Field cancerization. Field cancerization is defined as the presence of one or more mucosal areas consisting of epithelial cells that have cancer-associated genetic or epigenetic alterations. A preneoplastic field (shown in *light pink*) is monoclonal in origin and does not show invasive growth or metastatic behavior, which are the hallmarks of an invasive carcinoma (*dark pink*). Field cancerization has been supported by molecular data and provides a theoretical explanation for multiple primaries. (Adapted from Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. *Nat Rev Cancer.* 2011;11(1):9–22.)

Cancer Stem Cells

When tumor cells are grown in vitro or in a xenograft model, only a small fraction of the cells have the ability to form a new tumor.[6,7] In HNSCC, isolation of a population of cells expressing surface marker CD44 and aldehyde dehydrogenase (ALDH) was shown to have significant tumorigenic

potential, whereas CD44(−) cells did not.[8] The cells that possess the necessary characteristics of self-renewal and differentiation have been termed “cancer stem cells.” They constitute a minority of the cells within the tumor itself but are responsible for much or all of its tumorigenicity. The ability of these cells to self-renew can provide a near-endless supply of new tumor cells, and the ability to differentiate in phenotypically diverse ways allows them to produce a heterogeneous population of cells. Their capacity to differentiate and produce cells with new properties has linked them to cancer initiation, treatment resistance, local tumor recurrence, and metastasis.[9] Meanwhile, due to their slow growth and ability to adapt, these cells are not easily targeted by radiotherapy or traditional chemotherapies. For example, after irradiation of breast or glioblastoma xenografts, cancer stem cells were found to be enriched in the surviving tumor tissue.[10,11] These surviving cancer stem cells were found to possess fewer reactive oxygen species (ROS) (mediators of radiation-induced damage) and activated DNA damage response/repair pathways in response to the radiotherapy. Knowledge of the biologic nature and response of stem cells has led to the hope of targeting these resistance mechanisms therapeutically.

Tumor Heterogeneity

Like most cancers, HNSCCs are not simply an aggregate of a genetically identical cell population, but are composed of cells with marked genetic and cellular heterogeneity (Fig. 2.2).[12] This unexpectedly high degree of heterogeneity is thought to result from a combination of genomic instability, clonal evolution, and the effects of diverse, highly selective, microenvironments within a cancer. Recent evidence indicates that cancer stem cells may be principally responsible[13,14] for creating a heterogeneous population of cells, but that clonal evolution and the effects of the tumor’s microenvironment act in a synergistic manner (i.e., the cancer stem cells themselves may undergo clonal evolution and be affected by local influences in the tumor environment). Higher levels of intracancer heterogeneity have also been correlated to tumor progression, poorer survival, and adverse outcomes in patients with HNSCC. Recently, levels of tumor heterogeneity, when factored with HPV status, were found to be useful in predicting clinical outcome[15] in HNSCC.

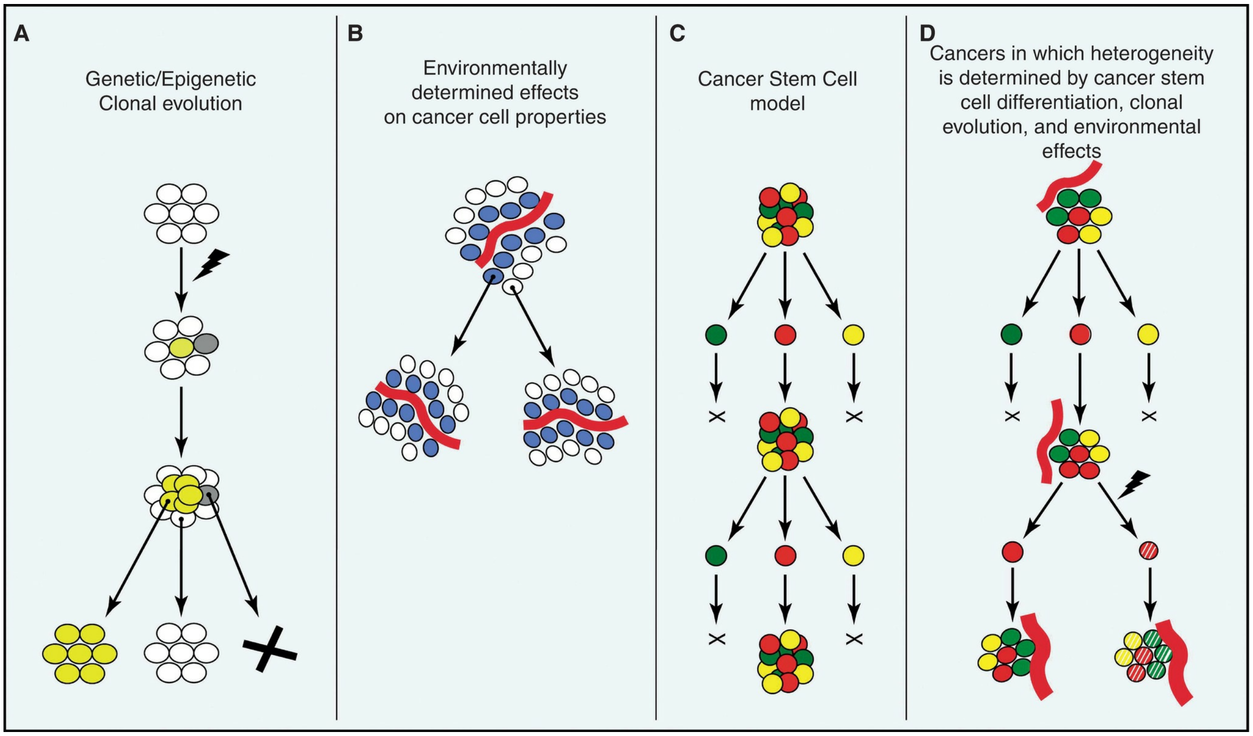


Figure 2.2. Tumor heterogeneity. Heterogeneity can arise within tumors through: **(A)** the stochastic process of clonal evolution, **(B)** extrinsic environmental differences within tumors, and **(C)** the presence of cancer stem cells that variably differentiate. These processes are not mutually exclusive, but rather synergistic in producing a heterogeneous population of cells **(D)**. (From Magee JA, Piskounova E, Morrison SJ. Cancer stem cells: impact, heterogeneity, and uncertainty. *Cancer Cell.* 2012;21(3):283–296, with permission.)

Intratumor heterogeneity makes it unlikely that a single biopsy will fully capture the histologic or genomic landscape of a patient's cancer. New methods have attempted to measure heterogeneity in an attempt to incorporate it into diagnostic workup and treatment, with the applications such as predicting metastatic potential, identifying treatment resistance, and predicting responses to targeted therapies. While performing multiple samples of a cancer (spatially or temporally spaced) may prove challenging and potentially dangerous, future efforts may focus on collecting the DNA of circulating cancer cells or even using molecular imaging to survey multiple areas of the cancer.[16]

RISK FACTORS AND ETIOLOGIC AGENTS

HNSCC has traditionally been, and continues to be, believed to be a cancer caused by environmental elements. Until the 1990s, almost all cancers of the head and neck were thought to be caused by tobacco-related carcinogens. Over the last 20 years, a remarkable shift has taken place, with the human papillomavirus (HPV) becoming responsible for a growing proportion of cancers of the head and neck, specifically of the oropharynx. HPV(−) and HPV(+) HNSCCs are now widely recognized as having distinct etiologies, risk factors, patient populations, clinical attributes, responses to therapy, and prognosis (Table 2.1). Given these observed clinical differences, it may come as no surprise that recent molecular analyses of hundreds of their cancers show a clear and marked distinction between HPV(+) and HPV(−) HNSCCs with regard to mutational profile, gene expression, methylation patterns, and signaling pathway activation.[21]–[24] The molecular and clinical differences between HPV(+) and HPV(−) tumors are clear indicators that we must no longer consider HNSCC as a single disease. Going forward, subtypes of HNSCC defined by the molecular characteristics of the tumor, as well as the genetic background of the patient, will guide therapy, with the goal of personalized cancer treatment. Accordingly, we explore HPV(−) and HPV(+) HNSCC separately in this chapter.

Table 2.1 Distinct Clinical Features of HPV(+) and HPV(−) HNSCC

Characteristic	HPV(–) HNSCC	HPV(+) HNSCC
Etiology/risk factors	Smoking, alcohol	HPV (high-risk sexual practices)
Incidence	Decreasing	Increasing
Age	Older	Younger
Gender	Male	Male
Race/ethnicity	AA > Caucasian > others	Caucasian > AA[a]
Socioeconomic status (SES)	Lower SES	No predilection
Site	All head and neck	Oropharynx
AJCC staging (TNM)	Higher T, lower N (79)	Lower T, higher N
Histopathology	Most commonly moderately to well-differentiated SCC, producing keratin (70)	Most commonly poorly differentiated or basaloid SCC, with koilocytes
p53	Inactivating mutations	Inhibited by E6
Rb	17p LOH, p16 mutation, deletion, or promoter hypermethylation	Inhibited by E7
p16 expression	Decreased	Increased
Chemoradiotherapy response	Good, but with high rate of recurrence	Good, with low rate of recurrence
Survival/recurrence	Poor for advanced stages	Good, but worse if smokers

[a]Data show a difference in racial/ethnic population affected by HPV(+) compared to HPV(−) HNSCC, though precise incidence rates have not been reported because data are from small cohort studies. (Gillison ML, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst.* 2008;100(6):407–420; Settle K, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. *Cancer Prev Res (Phila).* 2009;2(9):776–781. References 17, 18.)

AA, African American; AJCC, American Joint Committee on Cancer; LOH, loss of heterozygosity; N, lymph node stage; Others, Asian/Pacific Islander + American Indian/Alaska native + Hispanic; SCC, squamous cell carcinoma; SES, socioeconomic status; T, tumor size stage.

(Data sources: www.cdc.gov; Westra WH. The morphologic profile of HPV-related head and neck squamous carcinoma: implications for diagnosis, prognosis, and clinical management. *Head Neck Pathol.* 2012;6(suppl 1):S48–S54; Ang KK, Sturgis EM. Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. *Semin Radiat Oncol.* 2012;22(2):128–142. References 19, 20.)

Environmental Toxins

The vast majority of HPV(−) HNSCC are caused by exposure to environmental carcinogens. Fifty-five thousand HNSCC cases were estimated to occur in the United States in 2014.[25] The exact incidence of HPV(−) HNSCC is difficult to determine because HPV testing is not universal and reporting is not required. Long considered the traditional risk

factors, tobacco and alcohol are known to dramatically increase the risk of head and neck cancer.[26,27] While the risk from consumption of alcohol alone is modest, it synergistically increases risk when combined with tobacco.[28,29] In addition to the direct trauma to mucosal surfaces induced by these agents, tobacco products are composed of dozens of known carcinogenic compounds, including polycyclic aromatic hydrocarbons (PAHs), oxidizing substances, and free radicals. Following metabolic activation by endogenous enzymes (often cytochrome p450s), these carcinogens form covalent DNA adducts and/or induce epigenetic changes. These DNA adducts must be repaired by designated DNA repair machinery or else risk causing errors in replication (resulting in mutations).

Because many more people use tobacco than develop cancer, there are probably individual factors that moderate the risk of cancer development following exposure to the more than 60 known carcinogens in tobacco smoke.[30] The role of individual factors as modulators of the risk of cancer development has been examined with a focus on enzymes that metabolize the carcinogens. For example, the increased incidence of HNSCC in first-degree relatives of patients who have HNSCC supports a role for genetic predisposition that could be related to carcinogen metabolism.[31] Studies of gene–environment interactions are difficult and frequently underpowered, and in the case of tobacco carcinogen detoxification, the genes implicated exist in large families, which functionally overlap. Despite these constraints, polymorphisms in glutathione-*S* transferase (GST) and uridine 5′-diphosphate-glucuronosyltransferase (UGT) have been identified as possible risk factors.[32,33] That being said, the overall increased risk attributable to the presence or absence of any detoxifying enzyme polymorphism is modest, and mechanisms for translating knowledge of polymorphisms into decreased risk are not clear. As has been proven by recent decreases in cancer incidence,[25] a more fruitful area for impact is advocacy and education to decrease the use of tobacco.

Human Papillomavirus

HPV was first linked to cervical carcinogenesis in the 1970s by Professor Harald zur Hausen. The idea of a virus causing cancer went against the prevailing views of that time, and he was awarded the Nobel Prize in Medicine for this important discovery in 2008.[34] Soon after, an association

between HPV and head and neck malignancies was demonstrated when HPV antigens were detected in preserved histologic specimens.[35] However, it remained unclear if the HPV in these cancers was truly a causative agent or simply a passenger or contaminant. More recently, multiple lines of evidence have shown that HPV can be causative of HNSCC, particularly those arising in lymphatic-associated epithelium of the palatine and lingual tonsils. Epidemiologic data show that since the 1980s, there has been a decrease in the incidence of cancers of the head and neck in many developed countries, directly mirroring the decline in tobacco consumption. However, the incidence of cancer of the head and neck in nonsmokers has increased dramatically, along with the incidence of HPV-related cancers.[36] High-risk HPV is now causatively linked to the majority of oropharyngeal squamous cell carcinomas (OPSCCs).[37] Known aspects of HPV biology and mechanism of malignant transformation, as well as differences between HPV(+) and HPV(−) HNSCCs, will be discussed in depth later in this chapter.

Familial Disorders

As opposed to the modestly increased risk associated with polymorphisms in carcinogen-metabolizing enzymes, the risk of developing cancer in patients with familial cancer syndromes is dramatically increased. Fanconi anemia (FA) is an autosomal recessive disorder caused by mutations in any of a number of DNA repair genes (including the FANC and BRCA genes) that are primarily responsible for double-strand break repair. Disruption of these genes leads to chromosomal instability, an abnormally large number of mutations, and susceptibility to DNA-damaging agents. About 3% of patients with FA develop HNSCC, which represents a 700-fold increase over the general population.[38] Fanconi patients are also at a 50-fold increased risk for all cancers combined and are particularly susceptible to cancers caused by HPV,[39] leading to the hypothesis that the DNA damage response may be required for repairing DNA defects caused by HPV. Alternatively, defective DNA repair could accelerate HPV-driven tumorigenesis, HPV replication, or tolerance of HPV DNA. While DNA damage is considered an important component in the development of all types of solid tumors, it is unclear why HNSCCs represent such a high proportion of cancers in these individuals. Other familial disorders that predispose to HNSCC are Bloom syndrome, Lynch II syndrome, xeroderma pigmentosum, ataxia telangiectasia, and Li-

Fraumeni syndrome—all of which are associated with DNA damage repair deficiencies (Table 2.2). This underscores the critical role that DNA damage plays in HNSCC carcinogenesis.

Table 2.2 Familial Syndromes and HNSCC

Syndrome	Gene Affected (Function)	Risk of HNSCC	Other Associated Cancers	Other Characteristics
Fanconi anemia	FANC (DNA repair)	500-fold increased	Hematologic	Growth retardation, café au lait spots, skeletal malformations, bone marrow failure, renal anomalies
FAMMM	CDKN2A (cell cycle control)	Described rarely in families	Melanoma, pancreas	Familial melanoma/atypical nevi, early-onset pancreatic cancer
Bloom syndrome	BLM (DNA helicase)	Moderately increased	Leukemia, lymphoma, other carcinomas	Dwarfism, sun-induced skin rash, café au lait spots, facial abnormalities (normal IQ), immunodeficiency
Xeroderma pigmentosum	XP-A to XP-G (DNA repair)	Moderately increased	UV-induced skin cancer	Severe photosensitivity, ocular problems, neurologic problems (retardation, neuropathies)
Ataxia telangiectasia	ATM (DNA damage detection/repair)	Moderately increased	Leukemia, lymphoma	Progressive ataxia, telangiectasias, immunodeficiency
Li-Fraumeni	p53 (cell cycle, DNA damage response, others)	Moderately increased	Sarcoma, breast, glioblastoma, leukemia, lymphoma	No other associated abnormalities

FAMMM, familial atypical multiple mole melanoma syndrome; UV, ultraviolet radiation.

(From van Monsjou HS, et al. Head and neck squamous cell carcinoma in young patients. *Oral Oncol.* 2013;49(12):1097–1102. Reference 40.)

The CDKN2A gene encodes a protein ($p16^{INK4a}$) important in cell cycle regulation, as detailed later. Loss of functional $p16^{INK4a}$ by deletion, mutation, or promoter methylation is found in more than half of all cancers of the head and neck. Interestingly, families with germline $p16^{INK4a}$ mutations also have a very high incidence of malignancies, including melanoma, pancreatic cancer, and HNSCC.[41–45] Overall, due to the rarity of these predisposing syndromes and germline mutations, patients with HNSCC with these syndromes constitute a very small percentage of all HNSCC.

Prevention

Treatment and detection of HNSCC has become more sophisticated over the past few decades. However, primary prevention, early detection, and close surveillance of those at highest risk remain the strategies with the most impact to reduce morbidity and mortality from the disease. Clinicians are

among those responsible for communicating the importance of minimizing exposure to traditional risk factors such as tobacco and alcohol. Additionally, encouraging awareness of the signs/symptoms of cancers of the head and neck, implementing head and neck screenings, and improving access to appropriate health care can help diagnose these cancers at earlier stages as well as afford opportunities to initiate discussion regarding the risk factors for the disease.

Approved HPV vaccines are effective in preventing new infections from the HPV genotypes linked with cancer of the cervix and head and neck, and it is expected that the vaccine will have a major impact on the prevalence of both types of cancers. It is the responsibility of health care professionals to ensure that male and female children, adolescents, and other candidates receive the potentially lifesaving vaccine. The number of sexual partners and type of sexual practices are risk factors for HPV-related head and neck malignancies, so limiting risky sexual practices also minimizes risk in nonvaccinated individuals.[17]

TYPES OF GENETIC ALTERATIONS IN HNSCC

As is true for all cancers, genetic defects are at the root of carcinogenesis in the head and neck. Genetic defects leading to cancer can be inherited or acquired through defective DNA replication or repair, exposure to mutagens/carcinogens, or infection by microorganisms and viruses. The initiation and progression of cancer involves a stepwise accumulation of these genetic insults (or “hits”). These “hits” are usually alterations in tumor suppressor genes or oncogenes. They can accumulate in many forms, including mutations, copy number variations (CNVs), epigenetic changes, and others. We will discuss the alterations that contribute to development or progression of HNSCC (Fig. 2.3). While genes such as p53 and p16 are altered in the vast majority of HNSCCs, most affected genes in HNSCC occur in fewer than 30% of the cancers. Despite the enormous number of potential alterations, they tend to cluster in a limited number of biologic pathways, which helps to organize and understand the pathogenesis, and will be discussed afterward.

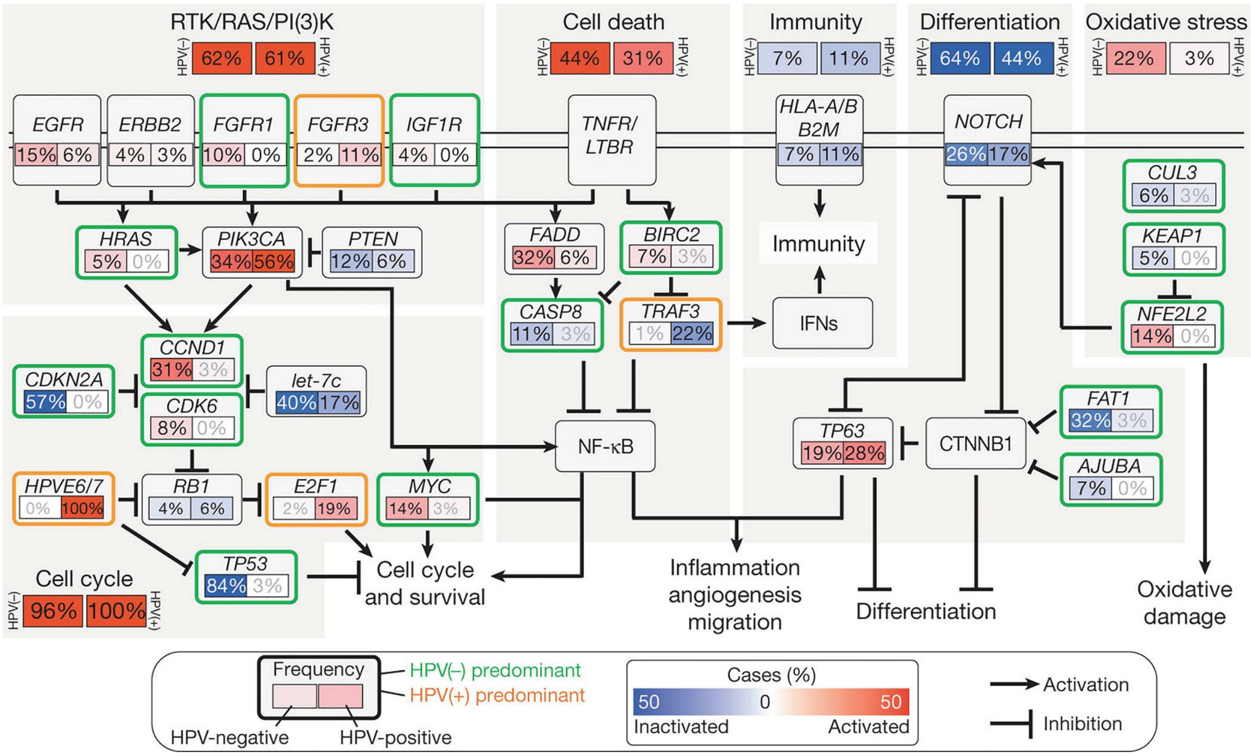


Figure 2.3. Pathways affected in HNSCC. Signaling pathways frequently altered in HNSCC, based on recent TCGA analysis. The frequency (%) of genetic alterations for HPV(−) and HPV(+) tumors is shown separately within subpanels and highlighted. (From The Cancer Genome Atlas N. Comprehensive genomic characterization of squamous cell carcinoma of the head and neck. *Nature*. 2015;517(7536):576–582, with permission.)

Mutations

Mutations describe alterations in the sequence of DNA itself and can occur in the form of nucleotide substitutions, deletions, or insertions. Their effect on the function of the protein is variable, as they may be categorized as silent (causing no change in the encoded protein), missense (leading to an altered amino acid sequence), or nonsense (truncation of the protein). The mutational landscape of HNSCC is being increasingly revealed by high-throughput, “next-generation sequencing.” HNSCC is associated with one of the highest mutation rates of any cancer, possibly due to the association of these tumors with environmental carcinogens known to induce DNA damage. Though there are a few characteristic mutations in HNSCC (Table 2.3), there is a large amount of genetic variability between tumors. Tumor suppressors including p53 (71%), CDKN2A (22%), FAT1 (23%), and NOTCH1 (20%)

are the most frequently mutated genes in HNSCC, with only one oncogene (PIK3CA, 21%) having a mutation rate >20%.[21] These frequently mutated genes map to a diverse set of biologic pathways including DNA repair (p53), cell cycle regulation (p53, CDKN2A), apoptosis (p53, PIK3CA), and cell differentiation (NOTCH1). Importantly, the mutational landscapes of HPV(−) and HPV(+) HNSCCs are quite different (Table 2.3),[46] as will be discussed later.

Table 2.3 Common Gene Defects in HNSCC

Oncogenes	**% HPV(+) tumors**	**% HPV(–) tumors**
PIK3CA	20 + 28 + 8 = 56	16 + 14 + 4 = 34
CCND1	3	31
EGFR	6	11 + 3 + 1 = 15
MYC	3	14
FGFR1	10	—
ERBB2	3	3 + 2 = 5
HRAS	—	5
Tumor suppressor genes	***% HPV(+) tumors***	***% HPV(–) tumors***
TP53	3	83 + 1 = 84
CDKN2A	—	33 + 25 = 58[a]
PTEN	3 + 3 = 6	2 + 10 = 12
NOTCH1	19	7
TRAF3	14 + 8 = 22	—
NSD1	—	10 + 2 = 12

Amplification; Activating mutations; Amplification and activating mutation;

Inactivating mutation; Deletion; Protein down-regulation; Total. The Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature*. 2015;517(7536):576–582. Reference 21.

[a]A significant proportion of HPV− tumors also display CDKN2A promoter hypermethylation (not shown).

Overall, it is clear that mutational changes drive cancer initiation and progression, but we are just beginning to understand the functional significance of many of them. Additionally, each tumor may have hundreds of mutations, and it can be difficult to determine the effect of each on the encoded protein, as well as whether a given mutation is a “driver” (directly causing carcinogenesis) or a “passenger” (having little impact on tumor cell fitness but co-occurring with driver mutations).

Copy Number Variations

A CNV consists of a structural change in a chromosome effecting a gain or loss of a portion of that chromosome, which can involve a single or multiple contiguous genes. They can come in the form of deletions, duplications, inversions, or translocations. Though prevalent in the normal human genome, CNVs that involve a loss of tumor suppressors or gain of oncogenes can predispose to neoplastic transformation. They can also result in a gene moving to come under the control of abnormal promoters or regulatory elements (e.g., BCR-Abl—the Philadelphia chromosome). CNVs in cancer cells have historically been detected using cytogenetic techniques such as chromosomal banding or fluorescent in situ hybridization (FISH), but next-generation sequencing has accelerated detection of CNVs and fostered an understanding of their crucial role in cancer.

CNVs are important in the pathogenesis of HNSCC. Each HNSCC harbors on average over 100 altered copy number segments, indicating a high degree of genomic instability. In HNSCC, the most common alterations are gains in chromosomal regions 3q, 5p, and 8q and loss of 3p and 8p.[21] These particular segments are gained or lost with such frequency because of the growth/survival advantage they confer (due to loss of tumor suppressors or gain of oncogenes). In HNSCC, deleted chromosomal segments include known tumor suppressors such as FAT1, NOTCH1, SMAD4, and CDKN2A. Recurrently amplified regions often include receptor tyrosine kinases (RTKs)

involved in growth signaling (growth hormone receptors EGFR, FGFR1, and ERBB2). The 3q region that is frequently amplified contains oncogenes important for survival, squamous differentiation, and stemness (PIK3CA, p63, hTERT, and SOX2). Many CNVs observed in HNSCC are common to epithelial cancers occurring elsewhere in the body, suggesting a common underlying pathophysiology. For many CNVs, the driver behind the change is unknown. Often, several contiguous genes are affected, making it difficult to decipher which genes are drivers versus passengers.

HPV(+) tumors display a distinct pattern of CNVs compared to HPV(−) HNSCC. The differences in CNVs reflect unique selective pressures that occur in HPV(+) versus HPV(−) HNSCC. For example, HPV(+) tumors express the oncoproteins E6 and E7, which through their inactivation of p53 and Rb diminish the pressure to delete either p53 or p16 in HPV(+) cancers. On the other hand, some CNVs (such as 3q amplifications and 3p deletions) are shared between HPV(+) and HPV(−) HNSCCs and are thus likely required for maintenance of squamous cells regardless of the etiologic agent.

Epigenetics

Epigenetics is a broad term that refers to self-perpetuating changes in gene expression that do not affect the actual sequence of DNA. The most well-characterized epigenetic alterations are DNA methylation and histone modifications. By altering the nonsequence structure of DNA and the histones that package it, epigenetic modifications can make genes more or less accessible to activators of transcription and therefore modulate their expression. Methylation is the most frequently studied epigenetic change, partly because there are well-established methods to examine it. Promoter methylation, as well as global hypermethylation, has been shown to facilitate tumorigenesis by the silencing of tumor suppressors. In HNSCC, promoter methylation of genes such as CDKN2A (encoding $p16^{INK4a}$ and $p14^{ARF}$), DAPK, RASSF1A, RARB2, APC, and MGMT is often an early event during neoplastic progression.[47–49] It has been postulated that epigenetic changes are complementary to the genetic changes, for example, silencing a wild-type tumor suppressor allele when the other is inactivated by mutation.

Additionally, whole-exome sequencing studies have revealed that several of the genes responsible for histone modifications are recurrently mutated in HNSCC (e.g., EZH2, MLL2, MLL3, NSD1).[21,50,51] Mutations of these genes

result in aberrant chromatin structure and gene regulation. This finding also underscores the role that epigenetics plays in HNSCC tumorigenesis.

Studies have shown that HPV(+) HNSCCs have increased global methylation compared to HPV(−), and clustering based on methylation can predict HPV status.[52] The clinical implications of epigenetics in HNSCC have yet to be firmly established, but it is likely that certain methylation patterns will be prognostic of tumor aggressiveness and/or predictive of therapeutic response.[52] Increasing knowledge about epigenetics has also helped to produce a new group of rational therapeutics, targeting histone deacetylases (HDACs) and DNA methyl-transferases (DNMTs), aimed at reversing aberrant epigenetic changes.

In addition to epigenetic alterations, gene expression can be modified at the transcriptional and translation level by microRNAs (miRNAs). These are small ~20 nucleotide RNA oligonucleotides, which complementarily bind mRNA, altering its fate through one of several mechanisms.[53] Although miRNAs are a normal, evolutionarily conserved process in plant and animal cells, tumor cells up- or down-regulate certain miRNA, which can enhance malignant properties. In HNSCC, expression of specific miRNA are consistently altered to deregulate expression of genes involved in cell cycle regulation (e.g., PTEN, p21)[54] and other cancer-related processes (e.g., KRAS). Presence or absence of certain miRNA has been correlated to prognosis, metastatic likelihood, and resistance to treatment; however, most miRNAs have several targets,[55,56] and their analysis is complex. In the future, miRNA signatures may be applied to identify tumor-specific subtypes or to guide treatment. Techniques for efficient delivery of miRNAs are being developed in hopes that they can be used therapeutically.

LINKING GENETICS TO PATHWAYS

The recent developments of whole-exome sequencing and other high-throughput techniques have added a wealth of data to the large preexisting body of work in the molecular biology of HNSCC. Although these data have allowed a more complete picture of defects in HNSCC, they have also highlighted the complexity of its pathogenesis. Understanding the role of even a single gene requires integrating the various types of genetic and epigenetic changes that affect it in the cancers of different patients, the

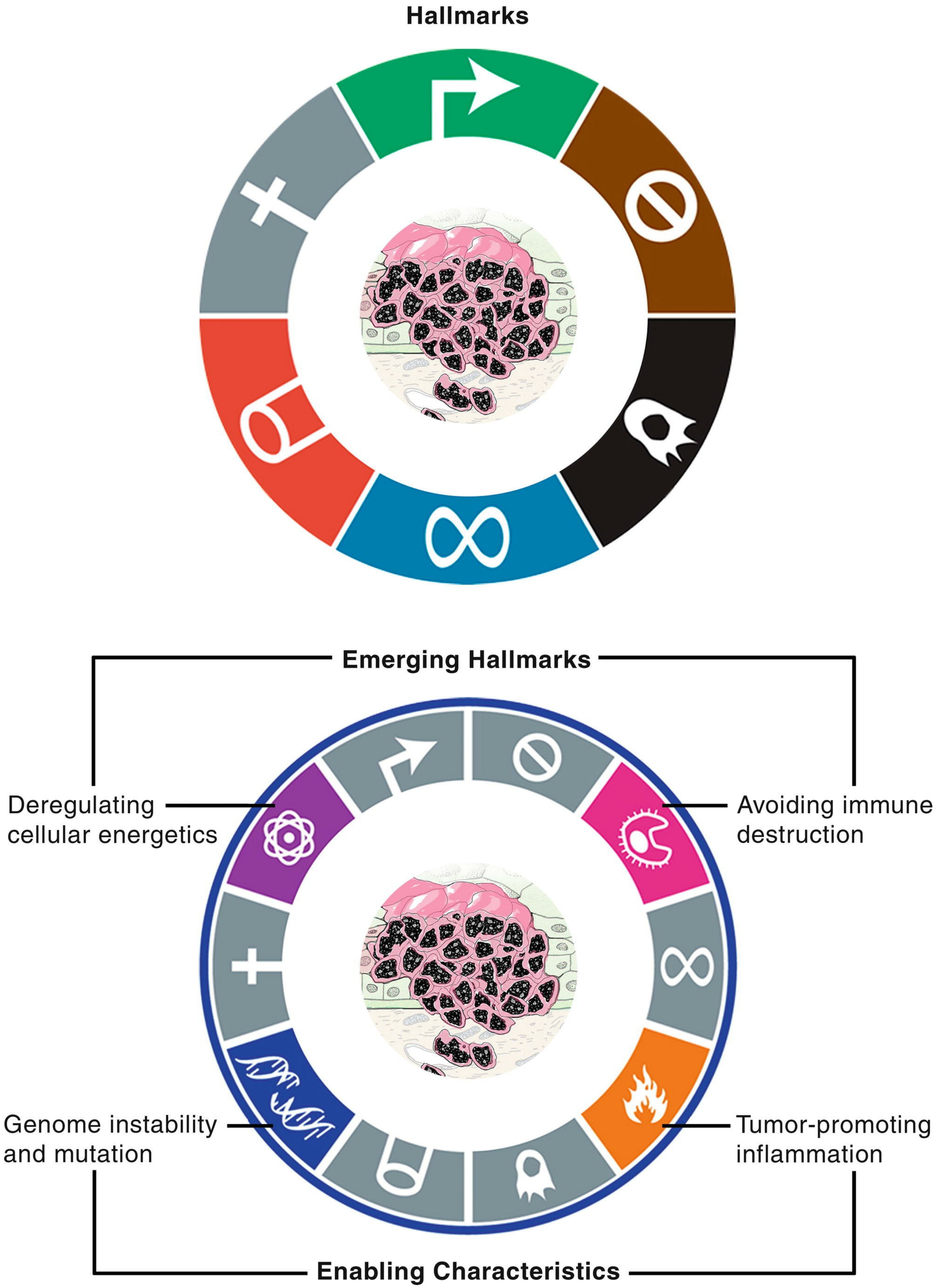
molecules it interacts with, and how the gene is affected over time and in spatially distinct areas of each patient's cancer. For example, though p53 itself is found to be mutated in around 70% of HNSCCs, it can also be deactivated in the remaining tumors by overexpression with or without amplification of MDM2 (which facilitates p53 degradation) or by expression of the HPV E6 oncoprotein. As the realm of tumor-related data has expanded to include mutations, amplifications/deletions, mRNA and protein expression profiles, microRNA expression, immune profiling, and epigenetic events, multiplatform data must be simultaneously considered to determine the drivers of carcinogenesis and direct therapy. Recent analyses suggest that data from different platforms carry overlapping information and omission of one type of data from multiplatform analyses does not necessarily alter classification.[57]

Categorizing defects into cancer-related biologic pathways can be a useful approach to organize and assign meaning to the wealth of data. For example, PIK3CA, a cell survival and growth gene, is mutated in 21% of a recent HNSCC cohort[21]; but when copy number amplifications were considered, that number rose to 36%, and when "hits" to other genes in the PIK3CA pathway were included, its pathway was affected in the majority of tumors.[21,58] For this reason, studies have shown that mutational data may be more useful when placed into pathways.[59] Though most of the early therapeutic successes in targeted cancer therapy have been based on individual mutations (e.g., BRAF in melanoma or EGFR in lung adenocarcinoma), understanding the mechanisms and pathways involved may help illuminate the most promising molecular targets for future treatments.

In the following section, we describe biologic pathways that are most commonly affected in HNSCC. Increasing knowledge of the normal function and interactions of these genes has laid a framework to fit the observed alterations into a narrative of cancer initiation and progression (Fig. 2.3). However, there is significant overlap and interaction between these pathways, and some pathways may be more affected in one tumor versus another. Genetically speaking, there are many different routes to cancer, which is why treating the disease in the future will likely require an equally sophisticated approach.

HALLMARKS OF HEAD AND NECK CANCER

In HNSCC, the transition of epithelial cells from normal to neoplastic involves a multistep process of accumulated genetic changes, which produces characteristic changes in biologic pathways that can be observed at the phenotypic level. The characteristic phenotypic changes, or “hallmarks,” seen in cancer cells have been frequently described and updated in recent years (Fig. 2.4).[60] We use these events as a framework to review the recent developments in the study of HNSCC. While we review the hallmarks with a focus on HNSCC, a comprehensive review can be found elsewhere.[60] The hallmarks discussed here include genomic instability, cellular proliferation, invasion and metastasis, angiogenesis, resisting cell death, replicative immortality, and reprogrammed metabolism. Additionally, interplay with the immune system (evasion of immune detection and tumor-promoting inflammation) will be discussed.



Hallmarks
Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting inflammation
Enabling Characteristics

Figure 2.4. Hallmarks of cancer. Hanahan and Weinberg initially described, then expanded, attributes needed for cancer development. (Adapted from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144(5):646–674.)

Genomic Instability

Normal cells possess a very high-fidelity system for DNA replication, such that errors occur once per 100,000 copied bases. Even those “rare errors” are corrected 99% of the time by DNA repair machinery, bringing the final error rate to one per ten million bases. A wide variety of systems known as “caretakers” detect and repair errors in the genome or, if unsuccessful, freeze the cell cycle and activate cell death.[61,62] Some mechanisms directly inactivate or intercept mutagens even before they damage DNA. The “clonal evolution theory” suggests that many alterations are needed for cells to gradually transform into cancer. Although the chances of this happening in a normal cell are infinitesimally small, damage to caretakers through genetic or epigenetic changes can lead to instability of the genome, increasing the error rate and allowing propagation of defects to subsequent generations of cells. Thus, by allowing the series of alterations required for neoplastic change, genomic instability is considered an enabling characteristic common to nearly all cancers.[63] The quintessential tumor suppressor p53 plays a central role in guarding the genome by activating DNA repair, cell cycle arrest, or apoptosis in response to genetic damage or cellular stresses.[64]

Endogenous and environmentally induced defects accumulate much faster without these proofreading capabilities, and although many of those genomic defects may be phenotypically silent, some (e.g., affecting tumor suppressors or oncogenes) will be involved in the carcinogenic processes described in the following sections. Across all cancers, HNSCC has among the highest levels of mutations, chromosomal rearrangements, and copy number alterations, highlighting the importance of instability within the genome to the pathogenesis of this disease.[65]

Dysregulation of Proliferative Signaling

Cells within normal tissues have a tightly regulated balance of proliferative and antiproliferative signaling that govern cellular growth and replication,

thus ensuring homeostasis between cell population and host resources. Progrowth signals most often come in the form of growth factors in the cells' environment that bind receptors on the cell surface and initiate signaling cascades within the cell. There also exist mechanisms to inhibit growth, ensuring that mitogenic signals are only transient and even inhibited in the presence of certain stimuli (such as DNA damage or absence of sufficient resources). Even in the presence of growth signals, cellular proliferation is tightly regulated, and cells must progress through many checkpoints and phases in the cell cycle in order to duplicate their DNA and divide into two daughter cells. In cancer cells, cell cycle checkpoints are universally circumvented to allow for aberrant cellular proliferation. One of the most fundamental characteristics of neoplastic cells is their ability to sustain proliferation, by either acquiring autonomous proliferative signaling or evading inhibitory mechanisms.

Progrowth Proliferative Signaling

Normal cells require a basal level of growth signals in order to survive and proliferate. Typically, growth factor molecules are released by distant or neighboring cells and bind to tyrosine kinase receptors on the cell surface, which relay that signal to a branching network of downstream effectors. By producing a growth factor ligand autonomously, increasing the quantity/efficiency of growth factor receptors, or constitutively activating downstream effectors, cancer cells routinely acquire autonomous growth signals.[66] In HNSCC, the epidermal growth factor receptor (EGFR) and its pathway are altered in a significant proportion of HNSCCs. Whereas mutations to the EGFR gene are uncommon, amplification and overexpression of EGFR are very common.[67] Other RTKs that are amplified or overexpressed and less frequently affected include hepatocyte growth factor receptor (MET), fibroblast growth factor receptor (FGFR), and insulin-like growth factor (IGFR).[21] Chief downstream effectors of growth factor receptors are also directly implicated in the pathogenesis of HNSCC, such as the PI3K/Akt/PTEN/mTOR,[58] JAK/STAT,[68] and RAS/RAF/MEK/MAPK pathways, each of which initiates a complex cascade of proliferative, survival, metabolic, or related functions.

Loss of growth inhibition is also common. Transforming growth factor beta (TGF-β) acts as an antiproliferative signal for normal epithelium, and its

downstream effector, SMAD4, is down-regulated in up to 20% of HNSCC.[21] As part of their greater functions as tumor suppressors, both Rb and p53 help to suppress proliferative activity as well. Although there is not a single growth factor or receptor that is universally altered in HNSCC, summation of various insults to the compilation of growth signaling pathways supports the concept that aberrant growth factor signaling is required for HNSCC development.

Cell Cycle

The normal cell cycle, the process by which cells replicate their DNA and divide, is guarded at various checkpoints to ensure that cells divide only when it is appropriate to do so (Fig. 2.5). The cell cycle consists of four phases: G1 (gap phase 1), S (DNA synthesis), G2 (gap phase 2), and M (mitosis). Progression through the cell cycle is mediated by activity of cyclin-dependent kinases (CDKs), interacting with cyclins. Additional regulation is introduced by expression of CDK inhibitors (CDKi) that can result in stalling of the cell cycle or permanent arrest. The quantity and phosphorylation status of cyclin–CDK complexes, as well as expression of CDKi, largely determine if a cell will initiate DNA replication and begin a round of the cell cycle. Proteins that regulate cell cycle progression are known as “gatekeepers” that prevent the cell from replicating unless conditions are appropriate. The tumor suppressors Rb and p53 are the canonical gatekeepers that halt cell proliferation in response to extracellular growth arrest signals or intracellular signals of DNA damage and resource limitations. They operate within complex circuits, which can also activate DNA repair or cell death if necessary. Gatekeepers must be circumvented for the aberrant cell cycle progression that occurs in cancer cells.

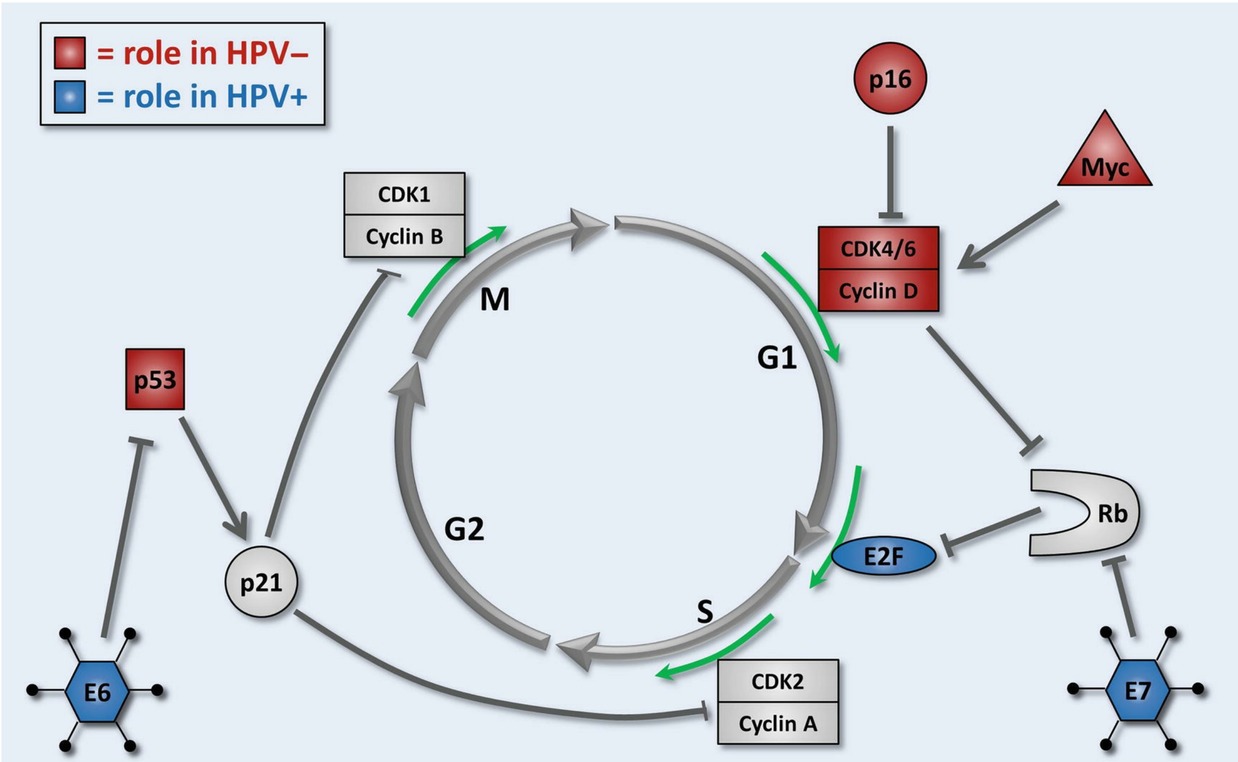


Figure 2.5. Cell cycle control. Progression through the cell cycle is tightly controlled in noncancer cells. In HNSCC, the regulators of cell cycle progression are ubiquitously altered by many different mechanisms. The most common defects in cell cycle regulators are shown for HPV− (*red*) and HPV+ (*blue*) HNSCCs.

As will be discussed later, p53 itself is mutated or deleted in roughly 70% of HNSCC. In most of the remaining 30% of cases, p53 is inactivated by the HPV E6 oncoprotein. Similarly, Rb activity is diminished through a variety of mechanisms in HNSCC. Although the Rb gene is mutated or deleted in only 5% of HNSCC, it is often directly inhibited by the HPV oncoprotein E7 or by alterations to its regulators (cyclin D1, p16^{INK4a}). The nearly ubiquitous, though heterogeneous, insults to the gatekeeper circuits indicate that this is one of the key requirements for development or progression of HNSCC.[69]

Abnormal Differentiation: Invasion and Metastasis

As part of their normal function, squamous epithelial cells express specific adhesion molecules in order to create a tightly packed functional sheet,

remain external to the basement membrane, and eventually terminally differentiate, senesce, and slough away. The normal maturation of epithelial cells involves orderly changes as they progress from the basal epithelial layer to become mature keratinocytes (Fig. 2.6). These changes are mediated by transcriptional changes driving increased or decreased expression of specific genes involved in epithelial differentiation. Disruption of this normal differentiation is thought to occur in HNSCC and other epithelial cancers, in which cell populations can attain properties and appearance of mesenchymal (connective tissue) cells. The resulting cells often lose their epithelial architecture, become less dependent on cell–cell contact, and possess increased motility, invasion, angiogenesis, and other mesenchymal-like properties. This phenomenon is referred to as epithelial–mesenchymal transition (EMT). The process of EMT is mediated by four major transcription factors: Snail, Slug, Twist, and Zeb 1/2. EMT is a normal process that is used during embryogenesis and wound healing but is hijacked during carcinogenesis.

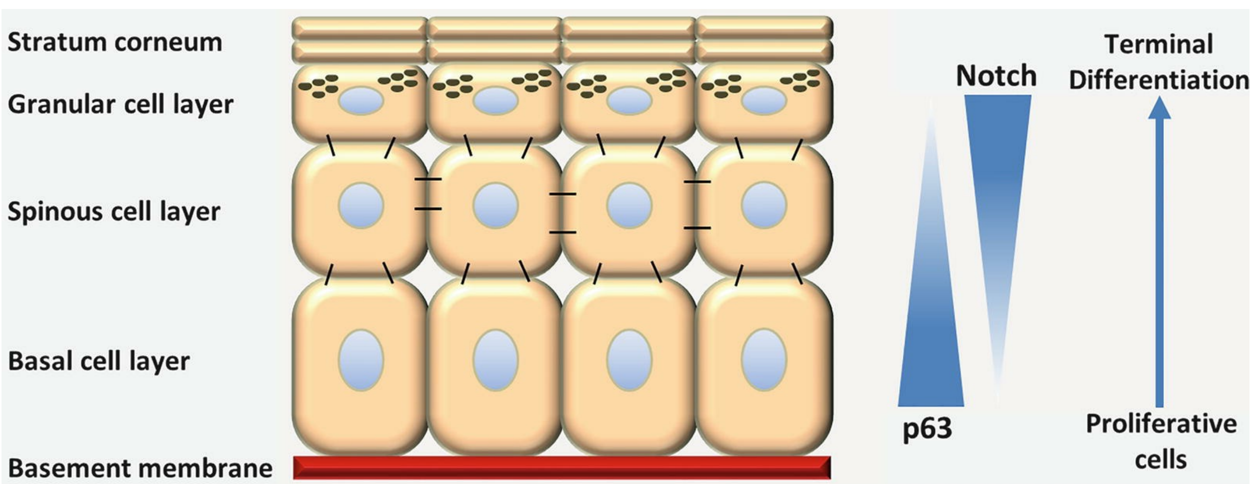


Figure 2.6. Maturation of keratinocytes. Epithelial cell proliferation is limited to the basal layer, and cells progressively differentiate as they migrate superficially before being sloughed from the surface. NOTCH and p63 play key roles in this differentiation process and are frequently disrupted during development of HNSCC.

Adherens junctions, a protein complex consisting of E-cadherin and α- and β-catenins, constitute a part of the normal cell–cell contacts between neighboring epithelial cells. They render the cells relatively immobile and

prevent cellular proliferation through a process known as contact inhibition. Compared to normal epithelium, cadherins are down-regulated in HNSCC.[70] Meanwhile, integrins, which help cells attach to the underlying extracellular matrix, are up-regulated in some HNSCC.[71] Beyond changes of adhesion properties, cancer cells have increased motility and invasion and possess matrix-degrading enzymes (matrix metalloproteinases—MMPs) (Fig. 2.7).[72,73] These changes are needed for the destructive invasive properties of HNSCC as well as for processes associated with lymphatic and hematogenous metastases.

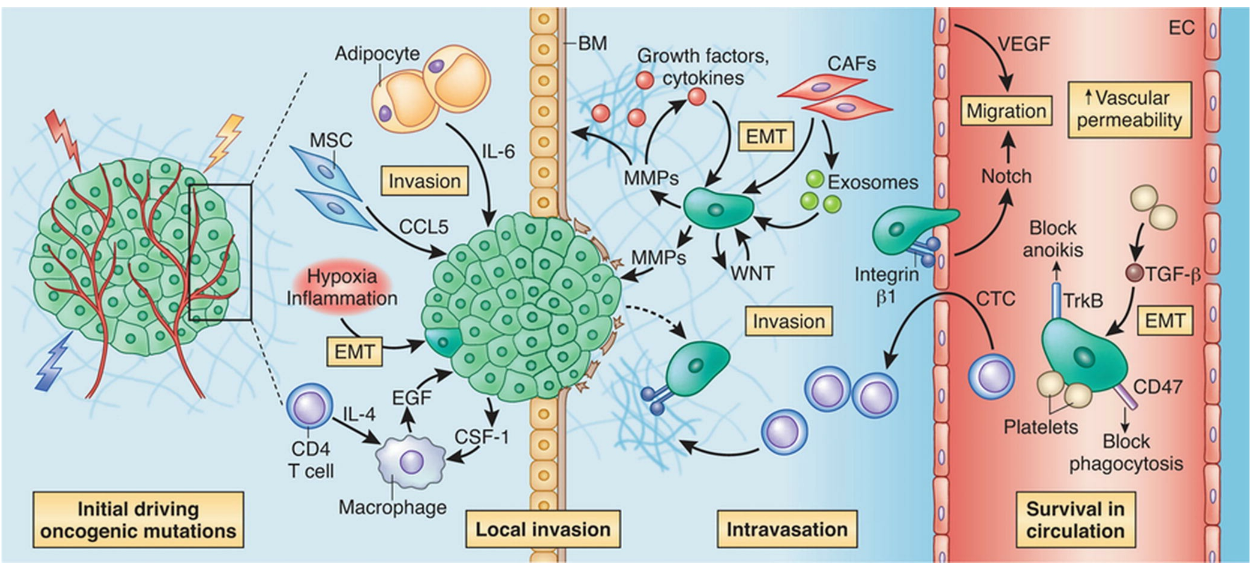


Figure 2.7. Tumor microenvironment, invasion, and metastasis. To disseminate, cancer cells acquire the capabilities to break down the basement membrane, invade into the stroma (local invasion), enter the blood circulation (intravasation), survive during dissemination, exit the blood vessel (extravasation, not shown) in a distant organ, and grow into clinically detectable metastases. In addition to cell autonomous mechanisms, cancer cells enlist a myriad of stromal cells to aid in each step during this invasion–dissemination cascade. BM, basement membrane; CAFs, cancer-associated fibroblasts; CTC, circulating cancer cell; EC, endothelial cells; EMT, epithelial–mesenchymal transition; MSC, muscle cells; MMPs, matrix metalloproteinases. (From Wan L, Pantel K, Kang Y. Tumor metastasis: moving new biological insights into the clinic. *Nat Med.* 2013;19(11):1450–1464, with permission.)

NOTCH is a family of transmembrane receptors that binds to the Delta and Jagged families of ligands on adjacent cells. When bound to its ligands, NOTCH is cleaved and the NOTCH intracellular domain (NICD) travels to the nucleus to affect gene transcription responsible for development and differentiation of a wide range of cell types, including epithelial cells. Although NOTCH was originally described as an oncogene, NOTCH signaling is down-regulated in HNSCC[74] as it is in several other squamous cancers.[75] Nineteen percent of HNSCCs possess a loss of function mutation in NOTCH1,[50,51] and a smaller percentage have loss of function in family members NOTCH2 and NOTCH3. In addition to its role in abnormal differentiation of HNSCC, aberrant NOTCH1 signaling simultaneously produces unchecked proliferation in many tumors. It is an elegant example of the interconnected nature of the "Hallmarks of Cancer." Another important gene involved in the differentiation of epithelial cells, p63, is overexpressed or mutated in 23% of HNSCCs.

Induction of Angiogenesis

As in normal tissues, cancers require oxygen, nutrients, and the removal of waste. A growing cancer demands high levels of energy and reducing capability, which can quickly outstrip nutrients and oxygen provided by the local blood supply. Hypoxia, as well as oncogene signaling, have been shown to drive the production of vascular endothelial growth factor (VEGF) and other factors that promote angiogenesis (Fig. 2.8). The neovasculature produced by tumor angiogenesis is characterized by excessive branching, erratic flow, and leakiness. Many HNSCCs overexpress VEGF or its receptors[76] resulting in a relatively high vessel density in HNSCC tumors.[77] Although not unique to HNSCC, the high density of leaky neovessels also provides a route of the spread of the cancer cells elsewhere in the body and can be considered an enabling factor for hematogenous metastasis. The cancers high requirement for nutrients also provides the basis for future antiangiogenic therapies, which have been tested in early clinical trials.[78]

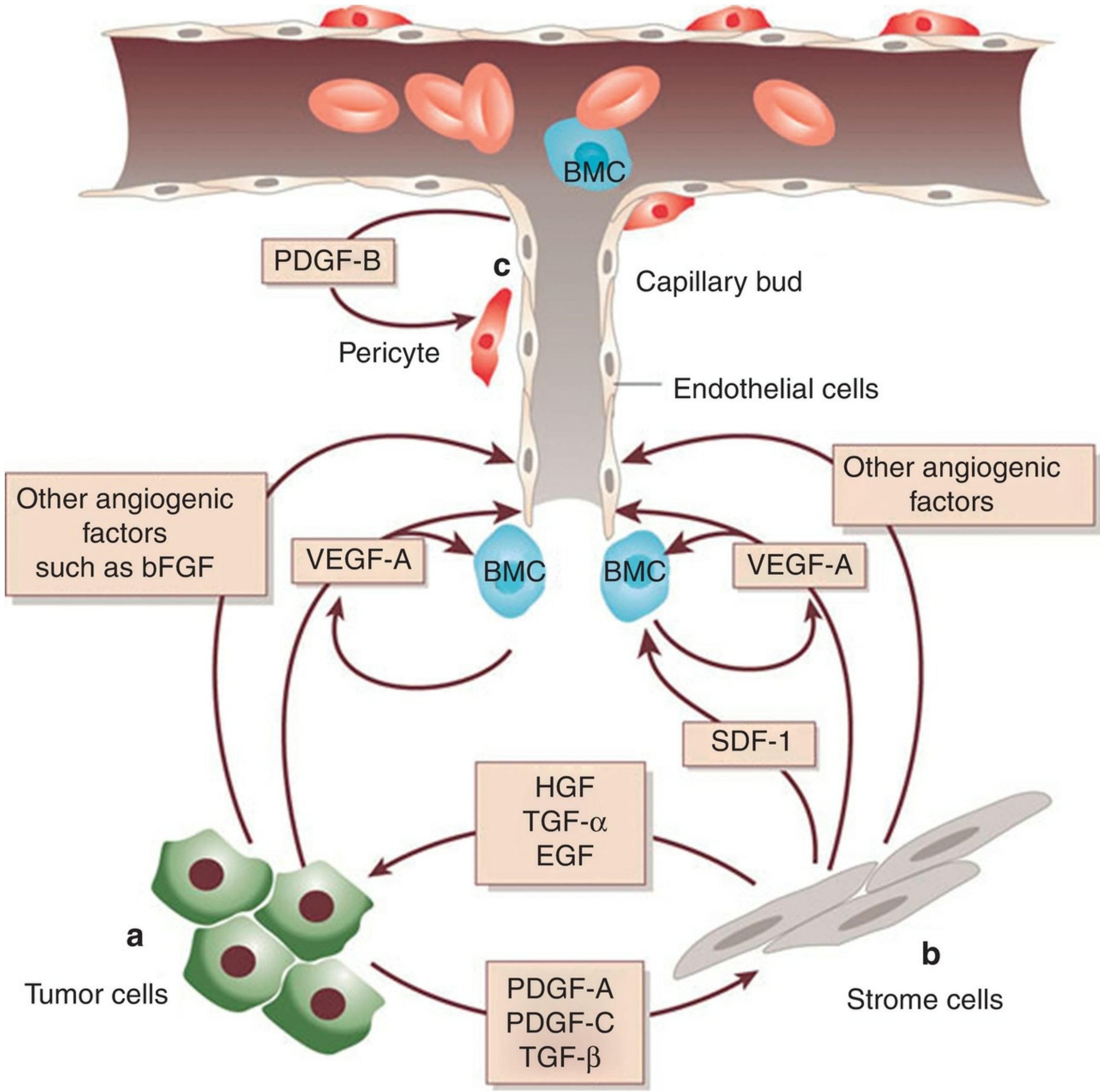


Figure 2.8. Angiogenesis. Cancer cells (a) produce VEGF and other angiogenic factors, which stimulate resident endothelial cells to proliferate and migrate. Stromal cells (b), such as fibroblasts, inflammatory, and immune cells, provide an additional source of angiogenic factors. Endothelial cells (c) produce PDGF-B, which promotes recruitment of pericytes in the microvasculature. Many of these angiogenic factors are being investigated as therapeutic targets. BMC, bone marrow–derived angiogenic cells; EGF, epidermal growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; SDF, stromal cell-derived factor; TGF, transforming growth factor; VEGF, vascular endothelial

growth factor. (From Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. *Nature*. 2005;438(7070):967–974, with permission.)

Resisting Cell Death

Apoptosis is a form of programmed cell death. Unlike necrosis, which consists of traumatic, acute cell death with the release of cell contents into the local environment, apoptosis involves an orderly, controlled process that results in fragments of the cell being phagocytized by neighboring cells. Apoptosis can be triggered through either the intrinsic pathway or the extrinsic pathway, which eventually converge on a common effector pathway (Fig. 2.9). In the intrinsic pathway, cell stresses such as DNA damage, decreased oxygen, or oncogene activation, activate p53 and result in transcription of various proapoptotic factors. A balance of proapoptotic (Bak, Bax) and antiapoptotic (Bcl-2, Bcl-xl) regulators determines whether the cell proceeds to apoptosis. When activated, proapoptotic factors migrate to the mitochondria and facilitate the release of cytochrome c, which in turn initiates the caspase cascade. The extrinsic pathway consists of external death signals in the form of specific ligands (e.g., Fas ligand), which bind to transmembrane receptors (e.g., Fas receptor) on the cells surface, which then recruits and activates caspase 8 to begin the caspase cascade. Both the extrinsic and intrinsic pathways converge on a common chain of effector caspases (3, 6, and 7), which initiate a proteolytic cascade resulting in a disassembly of organelles and consumption by neighboring cells.

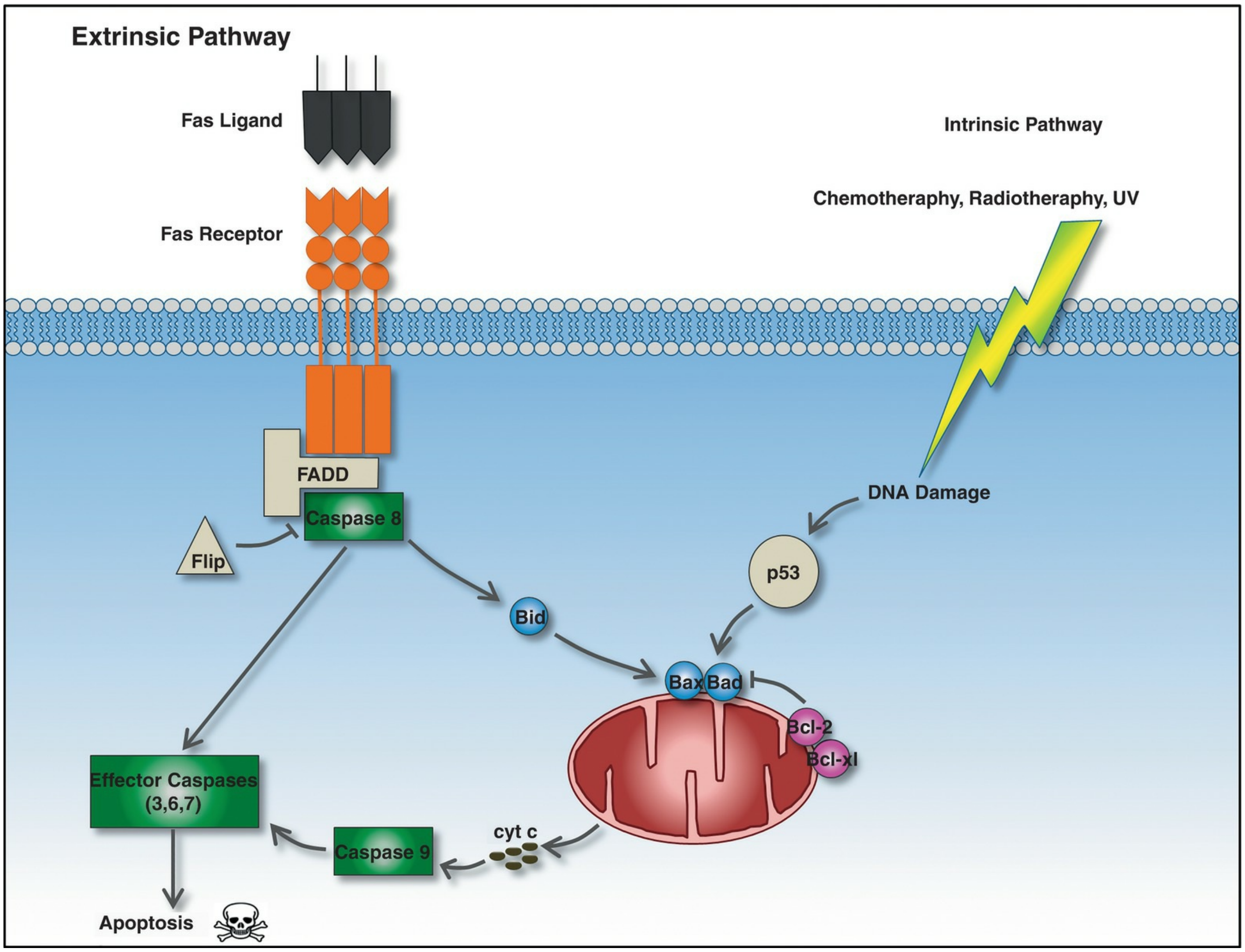


Figure 2.9. Apoptosis. The extrinsic and intrinsic pathways of apoptosis converge to activate controlled cell death. UV, ultraviolet radiation; Cyt c, cytochrome c.

Apoptosis serves as a major cell barrier to cancer.[79] As potential cancer cells acquire more and more molecular defects, these defects are more likely to be recognized and apoptosis triggered. There is always a balance between apoptosis and proliferation in tumors; however, for cancers, this balance must always favor survival and proliferation.[79,80] Thus, cancer cells usually evolve mechanisms to inhibit proapoptotic signals or up-regulate antiapoptotic signals. Loss of p53 activity is the most common defect limiting apoptosis in tumors, but increased expression or activity of antiapoptotic regulators (e.g., Bcl-2, Bcl-xL) or decreased expression or activity of proapoptotic factors is commonly found (e.g., Bax, Bak, caspases). Bcl-xL is up-regulated in 14% of HNSCC,[21] and caspase 8 (CASP8) is mutated or deleted in 10% of HNSCC. Interestingly, some cancers with CASP8 mutations maintain wild-type p53,

suggesting that CASP8 mutations may partially compensate for the presence of p53. As a prime example of the complexity of cancer signaling, proliferative pathways also inhibit apoptosis and promote cell survival. For example, EGFR signaling, PI3K/Akt signaling, and STAT3 activity have all been implicated in cell survival.[81,82]

As a mediator of chemotherapy- and cisplatin-induced cell death, apoptosis is targeted in order to increase efficacy of these treatments.[83,84] For example, inhibiting the antiapoptotic factor Bcl-xL has been shown to reduce cisplatin resistance.[85] Other studies targeting the p53 or survivin genes to increase apoptotic activity have also shown potential for synergistic antitumor activity with cisplatin.[86,87]

Replicative Immortality

With successive cycles of growth and division, normal cells eventually reach replicative senescence, a long-term state of viability without proliferation. Thus, normal, non–stem cells cannot multiply infinitely, and this poses yet another intrinsic barrier to cancer. It has been shown in the past few decades that telomere shortening and p16 expression contribute to this aging phenomenon.[88] Telomeres are repetitive nucleotide sequences at the end of chromosomes that protect the DNA ends from aberrant changes. However, telomeres shorten with successive generations, eventually becoming unable to prevent chromosomal damage such as end-to-end fusions. If unable to repair these telomere-associated chromosomal defects, the cell will die. Cancer cells must overcome this otherwise inevitable fate in order to secure immortality, and they do so by activating telomerase and inactivating p16 or Rb (Fig. 2.10). Telomerase is an enzyme that increases the length of telomeres, thereby reversing “aging” of the cell. Telomerase is nearly nonexistent in normal, mortal cells but expressed at high levels in the majority of immortalized cells in culture. As expected, increased telomerase activity is found in the vast majority of HNSCC tumors.[89,90] It remains unclear how telomerase activity or telomere length correlates to clinical features of the disease.

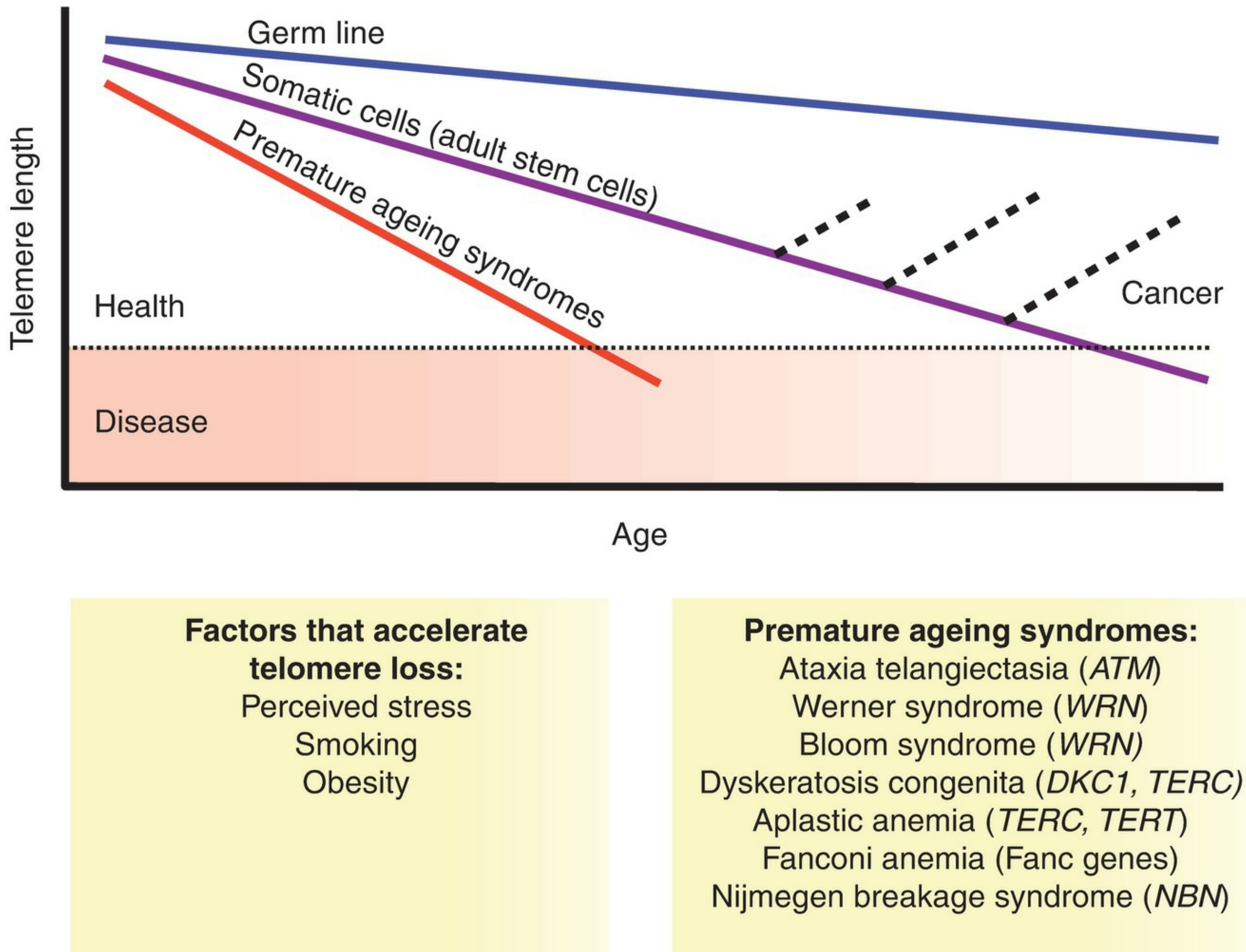


Figure 2.10. Immortalization. Normal somatic cells suffer progressive telomere attrition coupled to cell division or to increasing age of the organism. In germline cells, telomere shortening is attenuated owing to high levels of telomerase activity. By contrast, telomere shortening is accelerated in several human premature aging syndromes. In contrast, most immortalized cultured cell lines and human tumors aberrantly activate telomerase to achieve immortal growth. (Adapted from Finkel T, Serrano M, Blasco MA. The common biology of cancer and ageing. *Nature*. 2007;448(7155):767–774.)

Reprogramming Metabolism

As cancer cells proliferate, they must have a source of energy and building blocks for replication. It was discovered long ago that even in the presence of sufficient oxygen, cancer cells often preferred to utilize glycolysis as opposed to oxidative phosphorylation.[91] This was a curious finding, as glycolysis

represents a 20-fold reduction in efficiency compared to the Krebs cycle for producing ATP from glucose and is usually only performed out of necessity in the absence of oxygen. In order to fuel this “aerobic glycolysis,” cancer cells vastly increase glucose uptake by up-regulating glucose transporters, which is the basis for detection of HNSCC and many other cancers on PET-FDG (fluorodeoxyglucose) scans. Although less ATP is produced by glycolysis, the other by-products of glycolysis provide the building blocks and reducing capacity necessary for cell growth.[92] In addition, glycolysis results in production of lactate and acidification of the cancer environment, which in turn stimulates migration, provides a growth stimulus for surrounding tumor cells, and inhibits local immune function.[93]

With their uncontrolled proliferation, cancer cells have the capacity to outgrow their blood supply. Thus, these cells have adapted to thrive in hypoxic conditions. In response to hypoxia, they activate the transcription factor hypoxia-inducible factor (HIF), which further induces glycolysis and increases glucose uptake. Similarly, certain oncogenes themselves have been shown to up-regulate HIF and glycolytic metabolism. Various studies have revealed that HNSCC is associated with increased hypoxia and anaerobic metabolism.[94] Additionally, hypoxia in HNSCC has been suggested as a marker of poor prognosis,[95] as well as resistance to chemotherapy and radiotherapy.[96,97] It is postulated that the lack of oxygen prevents formation of therapeutic free radicals during radiotherapy and that the relative lack of perfusion results in decreased drug delivery during chemotherapy. Tumor metabolism is a growing area of research and may someday help explain these questions as well as clarify the relationship between metabolism and the other “Hallmarks.”

Role of the Immune System in Carcinogenesis

Evasion of Immune Destruction

Under normal circumstances, the immune system plays a vital role in the multifaceted process of cancer surveillance and destruction, at least partly explaining the significantly higher rate of tumors (including HNSCC) in various immunodeficient states.[98,99] Circulating cells of the innate immune system (natural killer cells, macrophages, dendritic cells) recognize local

tissue damage and products of necrotic tumor cells. Cytokines (such as interferon-gamma, IFN-γ) released by these processes further stimulate immune cells and have antitumor properties as well. Meanwhile, the adaptive immune system (T lymphocytes) can detect and destroy cells bearing cancer-specific antigens presented by HLA molecules.

It appears critical that in order for cancer cells to survive, they must evade surveillance and/or destruction by the immune system. They may do this by down-regulating expression machinery involved in antigen presentation.[100,101] The selective destruction of highly immunogenic clones may also gradually generate a cancer that is full of cells best suited to evade immune destruction, a process known as immunoediting.[102] It has been shown that HNSCC cells also secrete various factors that trigger T-cell anergy and even apoptosis.[103–105] Interestingly, HPV(+) cancers secrete different factors, including PDL-1, to accomplish a similar task.[106] The case of HPV(+) HNSCC is a special consideration for immune evasion; in addition to the need for cancer cells to avoid detection and destruction by adaptive immune responses, the viral infection and persistence must prevent cellular and innate immune responses. In addition to local secretion, HNSCC and other cancers release widespread factors and cytokines throughout the body, possibly signaling to hijack the host immunologic resources for the tumor's benefit of the cancer. As we learn more about the interaction of the immune system and cancer, it is clear that the relationship is not as simple as once thought.

Tumor-promoting Inflammation

Cancers of nearly every type are infiltrated by varying numbers of innate and adaptive immune cells. Although they may have been attracted to eliminate the cancer, experiments have shown that immune cells may actually spur carcinogenesis.[107–110] For example, DNA-damaging ROS released by immune cells to destroy a threat have been shown to increase genetic instability in tumor cells.[108] Additionally, immune cells attracted to fight the cancer may incidentally provide the cancer with a variety of growth/survival factors, proangiogenic factors, extracellular matrix-degrading factors, and factors that induce EMT. Although developed to combat exogenous threats, each of these may paradoxically enable cancer progression as part of the cancer's microenvironment.

Cancer Microenvironment

The cancer and its local environment, which consists of blood vessels, the extracellular matrix, signaling molecules, fibroblasts, neighboring cells, and immune cells, interact constantly and heavily influence one another (Fig. 2.7). For example, cancer can induce fibroblasts to begin secreting factors, which then support tumor growth and functions. The cancer's interaction with neighboring cells has also been proposed as the reason that cancers may be selective in the tissues to which they commonly metastasize (i.e., "seed and soil" hypothesis). The complex nature of the microenvironment presents a challenge to properly model and study HNSCC in the laboratory. Cells may behave differently, and certain drugs may be more or less effective in vitro than in the cells' natural, three-dimensional habitat. Knowledge of these interactions may identify new therapeutic targets (e.g., VEGF) or aid in the proper delivery of drug to tumors.

GENES ALTERED IN BOTH HPV(−) AND HPV(+) HNSCCS

p53

Arguably, p53 is the most widely studied tumor suppressor in human cancer and is the most commonly implicated gene in HNSCC as well. Located on the short arm of chromosome 17, TP53 is a 393 amino acid protein that is evolutionarily conserved and is expressed in all tissues of the body. The first 75 amino acids of TP53 are involved in the activation of transcription of specific genes, whereas amino acids 120 to 290 are involved in the specific recognition of DNA sequences.[111] The carboxyl terminus is believed to be important for nuclear localization and oligomerization of TP53 into tetramers.

The biologic role of p53 is to protect cells from DNA damage caused by radiation, chemical carcinogens, or other mechanisms. TP53 activity results in cell cycle arrest, so that DNA repair can occur, or by induction of apoptosis (Fig. 2.11). It performs these actions through the positive or negative regulation of gene transcription. Analysis of the sites of mutation of the TP53 gene in human cancers has revealed certain "hot spots" that are believed to be important in carrying out these functions. The majority of

mutations (more than 92%) are found in five evolutionary conserved regions of the gene. Mutations within these regions impair a cell's ability to repair its DNA, predisposing to genomic instability and additional alterations in oncogene and tumor suppressor gene products. Mutations of TP53 also prevent apoptosis in response to DNA damage, which may make cancer cells resistant to treatment with irradiation or chemotherapeutic agents that act by damaging cellular DNA and triggering apoptosis. The role of this gene in the pathogenesis of HNSCC has been extensively studied, but therapeutic activation of mutant p53 remains a future goal.

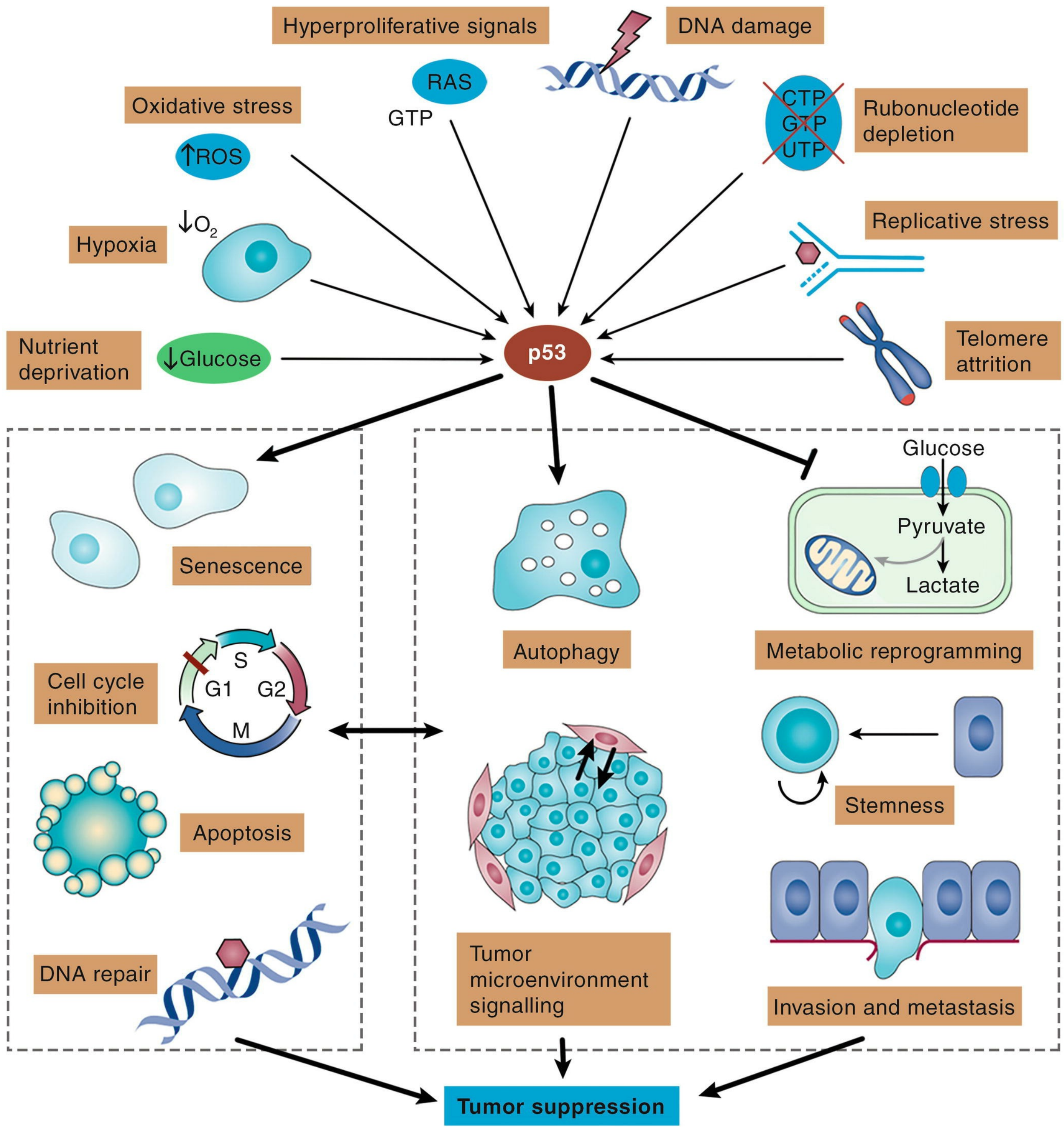


Figure 2.11. Functions of p53. Recent evidence demonstrates that a host of different stresses can activate p53 in the context of tumor initiation or progression (shown at **top**). P53 activation by these signals can consequently promote diverse responses that lead to tumor suppression (shown at **bottom**). (Adapted from Bieging KT, Mello SS, Attardi LD. Unravelling mechanisms of p53-mediated tumor suppression. *Nat Rev Cancer*. 2014;14(5):359–370.)

Early studies showed that aberrations in p53 were common in HNSCC

and increased in frequency during progression epithelium from normal, to hyperplastic, to dysplastic, to invasive cancer.[112,113] These studies also noted a correlation between p53 loss and genomic instability. P53 is now recognized as the most commonly mutated gene in HNSCC, with 84% of HPV(−) tumors having at least one mutation.[21] In the minority of HNSCCs expressing wild-type p53, there are alternative mechanisms for inhibition of p53 activity. First, in the roughly 20% of HNSCC that are HPV related, the HPV protein E6 binds to TP53, inactivates its function, and marks it for degradation, thereby abrogating the need for p53 mutation and accounting for the high incidence (97%[21]) of wild-type p53 in these cancers. Additionally, in the remainder (15% to 20%) of HPV(−) HNSCC with wild-type p53, it is proposed that the function of p53 is effectively inhibited by various (and potentially unknown) mechanisms. For example, the protein MDM2—which binds to the transcriptional domain of p53, blocks its activity, and marks it for degradation—is up-regulated in many cancers.[114] All told, these various insults to p53 occur in at least 95% of HNSCC, underscoring the importance of its pathway in the pathogenesis of the disease.

P53 mutation has been associated with poor patient survival in HNSCC, though early studies did not account for HPV status that may have confounded results.[115] More recent examination of HNSCC revealed that p53 mutations predicted to be disruptive were associated with increased local and regional recurrence.[116] Following knockdown of p53 expression, oral keratinocytes have increased ability to become immortalized.[117] Meanwhile, in addition to inactivation of its normal functions, some p53 mutations are associated with gain of function, as demonstrated by unique tumor phenotypes in genetically engineered mice.[118]

Because p53 is the most frequently mutated tumor suppressor across all human cancer types, restoring activity to mutant p53 has drawn much attention. Direct reactivation of mutant p53 using peptides to enhance normal conformation has shown biologic activity and therapeutic potential.[119] More recently, targeting compensatory proteins needed for cell survival in the absence of p53, such as WEE1[120] and aurora kinase,[121] have shown promise as targets for tumors with p53 mutations.

p16-Cyclin D1-RB

As with p53, inactivation of retinoblastoma (Rb) function is thought to be a requirement for human tumor formation. While defects in Rb are not common in HNSCC, its functional activity is diminished through a variety of other mechanisms (Fig. 2.5). In HPV(−) HNSCC, the most common defect inhibiting retinoblastoma is loss of activity of the tumor suppressor, $p16^{INK4a}$. $P16^{INK4a}$ is the most well-studied member of a family of INK4 (inhibitor of CDK4) proteins. $P16^{INK4a}$ binds and inhibits the G1 CDKs, CDK4 and CDK6, with resultant Rb activation and G1 cell cycle arrest.[122,123] Loss or mutation of $p16^{INK4a}$ results in excessive CDK activity and inactivation of Rb. All told, with 26% of tumors harboring $p16^{INK4a}$ mutations, 32% of tumors having homozygous gene deletion,[21] and 27% having expression lost through promoter hypermethylation,[124] down-regulation of the protein probably exists in the vast majority of HNSCC. The $p16^{INK4a}$ gene, CDKN2A, is also unique among human genes in that distinct first exons are spliced to a common second exon, but translation occurs in different reading frames resulting in two distinct proteins. Interestingly, protein products of the CDKN2A gene, $p16^{INK4a}$ and $p14^{ARF}$ (ARF, for alternate reading frame), are activators of RB and p53, respectively.[125,126]

The cyclin family of cellular proteins along with their partners, the CDKs, is responsible for driving the cell through the cell cycle. Of the many cell cycle regulators implicated in the development of cancers, cyclin D1 is among the most prevalent.[127] In HNSCC, CCND1, the gene that encodes cyclin D1 on the 11q13 locus, is amplified or overexpressed in up to 64% of tumors.[128] Studies have also correlated cyclin D1 expression with poor survival, invasion, locoregional recurrence, and the presence of lymph node metastases.[129–133] Aside from being a possible biomarker for disease phenotype, cyclin D1 has been extensively studied for therapeutic targeting.[134] Drugs that inhibit CDK 4/6 are showing promise for some cancer types, but primarily when combined with other agents.[134] Combinatorial therapy with CDK inhibition may be useful for HNSCC, because deregulation of G1 progression is nearly universal, but RB is still functional.

It is fascinating that the HPV oncoprotein E7 directly binds and inhibits Rb. While the details of this interaction will be explored later, this clearly obviates the need for genetic insults to the Rb pathway, as only ~5% of

HPV(+) cancers possess a defect in either p16 or cyclin D1. Overall, the extremely high rate and diverse nature of the alterations in the Rb pathway underscore the absolute necessity to bypass the G1 cell cycle checkpoint in order for cells to progress to HNSCC.

Pik3CA–PTEN–Akt

The PIK3CA gene encodes the catalytic subunit of the phosphatidylinositol 3-kinase (PI3K) protein, which adds phosphates to phosphatidylinositol, a membrane-associated lipid, producing phosphatidylinositol (3,4,5)-triphosphate that attracts proteins containing pleckstrin homology domains.[135,136] The major signaling pathway activated by PIK3CA is the protein kinase B (PKB = AKT) and mammalian target or rapamycin (mTOR) pathway, which supports cellular survival and growth. Normally, PIK3CA activity is stimulated by G proteins and RTKs. However, when mutated, PIK3CA remains active in the absence of upstream signaling.

Interestingly, PIK3CA is the oncogene most frequently mutated in HNSCC. Alterations in the PIK3CA gene have been discovered in 56% of HPV(+) and 34% of HPV(−) tumors. The majority of mutations (73%) are found in E542K, E545K, and H1047R/L hot spots and result in activation of the kinase, and the PIK3CA gene is located on the large 3q22-ter amplicon. Given that aberrations in other oncogenes occur less frequently in HNSCC, PIK3CA or downstream PI3K pathway components are perhaps the most promising therapeutic targets for both HPV(+) and HPV(−) HNSCC. Interestingly, in HPV(+) HNSCC, signaling of mutant PIK3CA activated mTOR more than AKT due to inhibition by E6, but in HPV(−) HNSCC, AKT and mTOR are both activated.[24]

Mutations in other components of the PIK3CA/AKT/mTOR pathway are common in other cancer types; however, mutations of PTEN and AKT are rare or not described in HNSCC. Given the importance of the pathway, drugs that target PIK3CA, AKT, and mTOR are excellent theoretical targets and are being tested for safety and efficacy in HNSCC.

COMMONLY AFFECTED GENES IN HPV(−) HNSCC

These are the individual genes most commonly implicated and extensively studied within HNSCC, and unless otherwise stated, these data specifically represent HPV(−) HNSCC. Each of the genes plays an important role in one or more of the "Hallmark pathways" introduced above, though the complex and interconnected nature of their functions often makes compartmentalization into a single pathway difficult. We present the data for each individual gene, integrating the various lines of evidence available in order to provide a comprehensive view of their role in HNSCC pathogenesis and/or progression. In addition to their critical roles in HNSCC carcinogenesis, many also represent avenues for targeted therapeutics and personalized treatments.

Tumor Suppressors in HPV(−) HNSCC

The most common defects in HPV(−) HNSCC are disruptions to tumor suppressor genes and are associated with defects in the regulation cellular proliferation, survival, and differentiation. Tumor suppressors have been difficult to directly target for therapy, because pharmacologic activation of mutant and inactive tumor suppressors is more difficult than inhibition of activated oncogenes. Recently, synthetic lethality schemes have been emerging for some defective tumor suppressors.

ARF

The ARF protein binds and inhibits MDM2, which is the major inhibitor of p53. MDM2 binds p53 inhibiting its transcription and marking it for proteasomal degradation. Inhibition of MDM2 by ARF stabilizes and activates p53.[125] The role of ARF in cancer development is clear in mice,[137] but is more questionable in humans.[138,139] Inactivating mutations of the CDKN2A gene selectively alter p16 activity; however, deletions of CDKN2A are common and result in loss of both p16 and ARF. Deletions of CDKN2A occur in HNSCCs with p53 inactivated by mutation, suggesting that the target of deletion is likely p16, not ARF.

NOTCH

NOTCH proteins are required for neural progenitor cell maintenance, and NOTCH is activated by chromosomal translocation in T-cell leukemias,

resulting in proliferation and survival.[140,141] On the other hand, NOTCH signaling is also required for epithelial differentiation,[142] and these dual roles suggest that NOTCH can serve as an oncogene or tumor suppressor depending on cellular context. In HNSCC, inactivating mutations in NOTCH1, NOTCH2, and NOTCH3 are observed in 31% of HPV(−) tumors.[50,51] NOTCH inactivation is also a common feature in lung and bladder squamous cancers, suggesting that loss of NOTCH is key for squamous carcinogenesis, possibly through inhibition of differentiation.[57] Targeting of NOTCH for cancer therapy is being explored for many cancer types but is currently limited to cancers where NOTCH acts as an oncogene.

Keap1/Nrf2

Keap1/Nrf2 are master regulators of cellular response to oxidative stress. Keap1 binds to Nrf2 and maintains Nrf2 in the cytoplasm in an inactive state. When exposed to oxidative stress, Nrf2 is released, translocates to the nucleus, and drives expression of many survival genes.[143] Interestingly, Nrf2, Keap1, and another critical component of the complex, Cul3, are altered in ~25% of HPV(−) HNSCC. The fact that defects are only observed in HPV(−) tumors suggests that cellular survival in high oxidative stress environments (e.g., tobacco smoke) promotes tumorigenesis.

Caspase 8

Caspase 8 is member of a family of enzymes responsible for triggering and executing apoptosis. Although there is cross talk between the intrinsic and extrinsic apoptotic pathways, caspase 8 is the final and critical step of the extrinsic pathway that is triggered by activation of the FAS receptor upon binding the FAS ligand. Caspase 8 cleaves and activates the executioner caspase 3 that leads to apoptotic cell death. Mutations of caspase 8 are found in 8% of HPV(−) HNSCC and remarkably ~1/3 of caspase 8 mutations are associated with mutations in the HRAS oncogene and occur in the absence of p53 mutations.[21] This subset of p53 wild-type tumors with simultaneous mutations of caspase 8 and HRAS is potentially targetable using apoptosis activators.

Oncogenes in HPV(−) HNSCC

Although activation of oncogenes is not as frequent in HNSCC as is disruption of tumor suppressors, they are of particular interest because of their therapeutic implications. In general, activating mutations or amplification of oncogenes has been easier to target with drugs to inhibit the abnormal activity. The successful targeting of the fused and activated ABL oncogene (Philadelphia chromosome) in chronic myeloid leukemia (CML) by imatinib opened the door for targeting of mutant oncogenes such as BRAF in melanoma, EGFR in adenocarcinoma of the lung, and others.

EGFR/RTKs

The EGFR and other members of the RTK family, such as human epidermal growth factor receptor 2 (HER2), have been as heavily studied as any oncogene in HNSCC. Extensive research and clinical trials resulted in approval of EGFR-targeting antibodies for therapy.[144] EGFR is amplified in 10% and overexpressed in many more HPV(−) HNSCCs, while HER2 is amplified in 3%.[21] Overexpression of RTKs is not seen in HPV(+) HNSCC. Interestingly, activating mutations of EGFR are relatively rare in HNSCC (5%), and drugs that have been effective in EGFR-mutated adenocarcinoma of the lung have not shown the same activity in HNSCC. How to appropriately target the EGFR family remains a focus of research, including combinatorial therapy and simultaneous targeting of other RTK family members such as the human epidermal growth factors 2 and 3 (HER2 and HER3).

The FGFR subfamily of RTKs is also frequently activated in HPV(−) HNSCC by amplification and overexpression. Members of the FGFR family, FGFR1, FGFR2, and FGFR3, are amplified in 10%, 2%, and 2% of HPV(−) HNSCC, respectively, and cumulatively overexpressed in another 14%.[21] Drugs that have activity against FGFR family members are in clinical trials for patients whose tumors carry alterations in FGFR.

p63

The p63 gene is another example of a gene product that has both tumor-promoting and tumor-suppressing activities. P63 is a homologue of p53. However, unlike p53, it has two major expressed forms. Transcriptionally, active p63 (TAp63) is a tumor suppressor with activities similar to p53,

whereas delta N p63 (ΔNp63) is missing the transcriptional activating N-terminal region and has anti-p53 activity.[145] ΔNp63 is the major p63 form implicated in HNSCC and is coamplified with genes on the 3q22-ter amplicon. High expression of ΔNp63 is observed in HNSCC and correlates with amplification of the 3q region that occurs in 19% of HNSCC.[21] The 3q amplicon contains a large number of genes in addition to p63, including those involved in survival (PIK3CA) and stem cell maintenance (SOX2).

RAS

The RAS (rat sarcoma) family of oncogenes is commonly activated in human cancers but has been difficult to target with drugs. Although there are three members of the RAS family in humans, only Harvey RAS (HRAS) is mutated in HNSCC, occurring in 5% of HPV(−) tumors.[21] Hot spot mutations of HRAS stabilize its binding to guanosine triphosphate (GTP) resulting in constitutive activation and cellular proliferation and survival that is independent of upstream signals. Because of its importance in multiple types of cancer and its difficulty in targeting, the National Cancer Institute has recently allocated resources to improve targeting of mutant RAS in cancer.

SOX2

Transcription factors are notoriously difficult to target for therapy, and the sex-determining region Y-box 2 (SOX2) gene product is no exception. SOX2 is a key driver of pluripotency or stemness and self-renewal of cells, and overexpression of SOX2 has been shown to promote lung squamous cell cancer in mice and has been associated with poor survival in HNSCC.[146,147] In HPV(−) HNSCC, SOX2 is amplified along with the 3q22-ter region in 19% of cancers, is one of the key drivers of cancer stemness, and will be a valuable target to inhibit the stem population.

HPV(+) HNSCC

The Papillomavirus subfamily, together with Polyomaviruses, creates the Papovaviridae—a family of DNA viruses often associated with malignant transformation of mammalian cells. Human papillomaviruses[148] are

associated with benign (e.g., papillomas, warts) and malignant lesions of keratinized and mucosal epithelial surfaces. Based on their potential to induce malignant transformation, more than 100 viral genotypes are subdivided into low- and high-risk HPVs. High-risk (oncogenic) genotypes, most commonly HPV types 16 and 18, as well as the more rarely encountered types 31, 33, 35, 39, 45, 51, 56, 58, and 59, are causative agents of anogenital cancers[149–151] and the majority of OPSCC[152–154] with HPV 16 being responsible for the vast majority of HPV-related HNSCC.[17] The incidence of HPV-related OPSCC has dramatically increased over the last two decades and is now approaching the incidence of uterine cervical cancer in the United States.[155–157]

Viral Biology and Epithelial Transformation

Papillomaviruses are sexually transmitted, species-specific, nonenveloped, double-stranded DNA viruses that have a roughly 8,000 base pair circular genome coding for 6 early (E) and two late (L) proteins. The viral genome is protected by a 55 nm icosahedral capsid[158–161] consisting of 72 capsomers, with each capsomer being a pentamer of the L1 major capsid protein. The minor capsid protein L2 is required for efficient viral DNA encapsidation and the generation of infectious virions.

Papillomaviruses infect proliferating undifferentiated keratinocytes in the basal layer of stratified epithelia. Studies of cervical stratified epithelia revealed that papillomavirus infects basal cells following trauma to the superficial layers. Viral protein synthesis is tightly regulated by cellular differentiation, because capsid proteins are not expressed in basal cells. As infected cells migrate to the surface and differentiate into keratinocytes, the major L1 and minor L2 capsid proteins are produced and the viral genome replicates, resulting in up to 10,000 viral DNA copies per cell, allowing virion assembly and shedding of infectious viral particles as differentiated epithelial cells are sloughed from the surface.[158,162–164] HPV is cleared by the immune system in the majority of infections, but if persistent, HPV can remain latent and form benign or malignant epithelial lesions. The host and viral factors that determine the specific outcome of the HPV infection are not well understood. During the course of an infection, the virus is eventually sloughed with epithelial cells in order to infect other organisms and complete its life cycle. Figure 2.12 shows a timeline for the progression from an initial

infection to a malignant tumor.

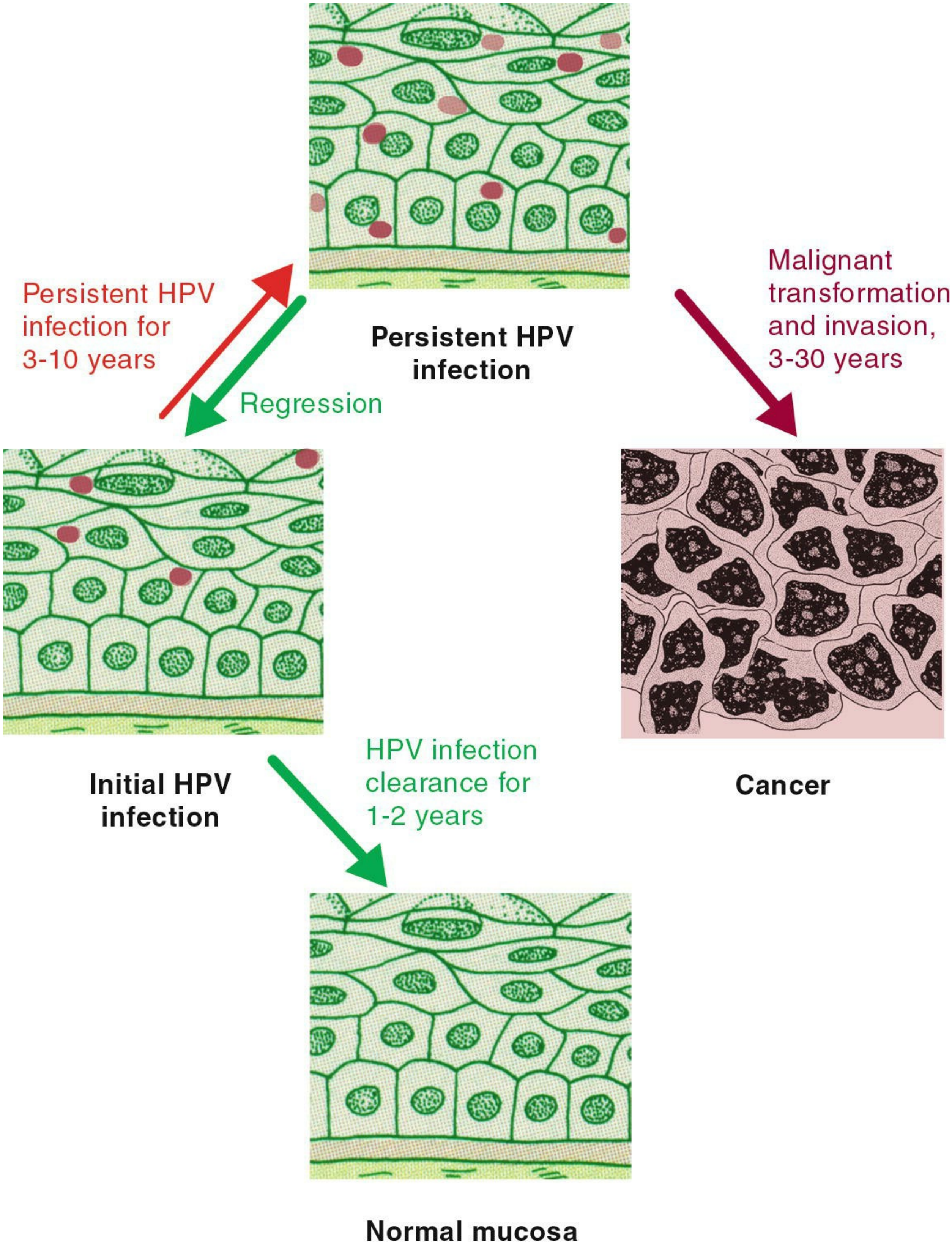


Figure 2.12. Timeline of HPV infection. An initial HPV infection can either be cleared or progress to a persistent infection lasting for years. Malignant transformation can result, usually many years after the initial infection. The host-, environmental-, and viral-related factors that determine the outcome of the HPV infection are not well understood.

Although great strides have been made to unravel the mechanisms by which high-risk HPV transforms normal cells, our knowledge of HPV-related carcinogenesis is incomplete. Nearly all studies examining HPV carcinogenesis have focused on cervical keratinocytes or the genital epithelia, with few examining oropharyngeal tumorigenesis. Development of uterine cervical cancer requires persistent viral infection and includes a well-described progression from precancerous lesions to invasive cancer. In early lesions, the HPV genome remains in an episomal state, but with advancement to high-grade lesions, HPV DNA frequently integrates into the host genome—a step that facilitates cancer development.[165,166] Integration is believed to accelerate carcinogenesis through frequent disruption of the HPV E2 gene, which normally suppresses expression of the major HPV oncogenes, E6 and E7.

The oncogenic properties of E6 and E7 are primarily explained by their abilities to inactivate two main human tumor suppressor proteins that are disrupted in virtually all human cancers: p53 and Rb. Inactivation of these targets deregulates cell cycle progression and inhibits apoptosis. E6, after forming a complex with cellular E6-associated protein (E6-AP), binds p53 and targets it for ubiquitination and subsequent proteasomal degradation. Several other E6 targets, including catalytic subunit of telomerase (hTERT), also contribute to E6-mediated transformation. E6 promotes cellular immortalization by up-regulating transcription of hTERT and can directly bind the hTERT protein to increase telomerase activity. Similar to E6, the HPV E7 protein functionally inactivates Rb via direct binding, ubiquitination and proteasome-dependent degradation. This results in the release and permanent activation of transcriptional factor E2F, driving expression of S-phase genes and promoting cellular replication. Interestingly, overexpression of another tumor suppressor, CDK inhibitor $p16^{INK4a}$, which is commonly observed in HPV(+) human cancer and is considered to be a surrogate marker for HPV positivity, is also linked to E7-mediated inactivation of Rb. In

human cancers, Rb inactivation is often reciprocal with p16 expression levels, indicating that down-regulation of Rb function is equivalent to loss of p16.[167]

Growing evidence suggests that the E5 protein in HPV types 16 and 18 also contributes to carcinogenesis. In transgenic mouse models, E5 alone induces cervical cancer and its tumorigenic effect synergizes with E6 and E7.[168] Although the exact mechanistic contribution of E5 to cancer development is not known, the role of HPV E5 in proliferation, migration, and invasion of cancer cells has been anticipated.[169]

Following HPV genome integration, E6 and E7 genes are consistently retained, whereas other HPV early and late genes are variably lost.[170] Due to integration and loss of part of the HPV genome, cervical malignant lesions are not thought to support an active HPV infection. However, some OPSCCs possess both integrated and episomal HPV DNA, whereas other tumors contain only one or the other.[171–174] Recent comprehensive whole-genome and transcriptome analysis of 35 HNSCC identified HPV integration in 25 cases (~71%),[175] confirming that HPV infection can drive development and progression of cancer of the head and neck independent of integration.

Syndromes Predisposing to HPV(+) HNSCC

As discussed previously, some familial syndromes caused by inherited mutations in genes involved in DNA repair and other vital cellular functions dramatically increase the relative risk of cancer of the head and neck (Table 2.2). Whether these genetic disorders predispose specifically to HPV-associated HNSCC remains inconclusive, with conflicting data reported by different research groups. In 2003, Kutler and coworkers[38] found HPV 16 in 83% of cancer of the head and neck in FA patients, as compared to 36% in the control population. In addition, an increased prevalence of HPV infection was found in the oral cavity of FA patients.[176] In contrast, several groups failed to detect HPV in HNSCCs from FA patients.[177–179]

Genomics of HPV(+) HNSCC

Expectedly, some specific molecular features arise as a result of expression of functional HPV oncogenes. As discussed, the HPV oncoproteins E6 and E7

inactivate p53 and Rb, respectively, and, therefore, HPV(+) head and neck tumors nearly universally harbor wild-type p53 and highly express the Rb upstream regulator p16^{INK4a} (CDKN2A). In addition, HPV(+) and (−) cancers are easily distinguished by gene expression profiling.[180–182] The great majority of genes differentially expressed in HPV(+) versus HPV(−) HNSCCs act in cell cycle, including CDK inhibitors 1B and 1C (CDKN1B/C), p15^{INK4b} (CDKN2B), transcriptional factors E2F1 to E2F4, and G1/S phase–specific kinase CDC7, as well as in DNA replication and DNA repair (DNA polymerases, minichromosome maintenance proteins 2 to 7, MCM2 to MCM7; X-ray repair cross-complementing protein, XRCC1; and replication protein A, RPA2).[180–182] Notably, all these genes are overexpressed in HPV(+) tumors compared to HPV(−) HNSCC.

In addition to genes, several miRNAs are up-regulated (miR-9-5p, miR-20b-5p) or down-regulated (miR-193b-3p) in HPV(+) OPSCC.[183,184] The contribution of these miRNA alterations in HPV-associated tumorigenesis are not well described, but are also seen in HPV-associated cancers of the urogenital tract.[184]

Losses of 3p and 8p, and gains of 3q and 8q chromosomal regions, are common in HNSCC, irrespective of HPV status. The 3q26/28 amplicon contains several genes that control epithelial cells differentiation and survival, including the TP53 homologue, TP63, SOX2, and the oncogene PIK3CA.

Notwithstanding chromosomal amplifications and deletion shared with HPV(−) HNSCC, HPV(+) cancers also possess a distinct signature of chromosomal gains and losses. Massive genome-wide analysis of HPV integration revealed a direct link between HPV integration and genomic rearrangements, including amplifications, deletions, and translocations. Interestingly, in the cohort of 25 HPV(+) HNSCC, no HPV integration sites were recurrent,[21,175] which may suggest a random mechanism of the integration event. Although not mechanistically linked to HPV integration, a recently discovered recurrent deletion of the TNF receptor-associated factor 3 (TRAF3) gene was identified in 14% of HPV(+) head and neck tumors, and truncating mutations of TRAF3 were also found in 8% of HPV(+) HNSCC. Remarkably, neither mutations nor deletions of TRAF3 were found among 243 analyzed HPV(−) HNSCC.[21,175] Exclusive alterations of TRAF3 in HPV-associated HNSCC along with the known role of TRAF3 in cellular

antiviral response strongly suggest that inhibition of TRAF3 function is critical for tumorigenesis driven by HPV in the head and neck. Interestingly, inhibition of TRAF3 is also observed in Epstein-Barr virus (EBV)-associated malignancies, but in this case, the EBV oncogenic protein, LMP1, interacts with TRAF family members. Further, TRAF3 deficient mice are predisposed to squamous cell carcinomas of the tongue and salivary gland tumors with an incidence as high as 50%.[185]

Another important genomic feature that differentiates HPV(+) from HPV(−) HNSCC is focal amplification of E2F1—a transcriptional factor driving cell cycle progression—found in 19% of HPV(+) head and neck tumors. The reason for E2F1 amplification in the face of HPV E7-driven inhibition of Rb and Rb-family members is unknown. E2F1 and its family member E2F2 have been implicated in amplification of the HPV genome, but the role of E2F1 in HPV(+) HNSCC remains speculative.[186]

The most common genetic events found in HPV(+) HNSCC are summarized in Table 2.3. Several previous studies have shown significantly fewer somatic mutations and fewer chromosomal abnormalities in HPV(+) as compared to HPV(−) HNSCC[22,23]; in contrast, recent TCGA analysis found that mutation rates did not depend on HPV status.[21] However, HPV(+) tumors showed specific global mutation signature enriched for the APOBEC-associated mutations. APOBEC is a family of cytidine deaminases that convert cytosine to uracil during RNA editing and retrovirus and retrotransposon inhibition. Recently, APOBEC family members have been shown to induce specific mutation clusters in a number of human tumors, including bladder, cervical, breast, head and neck, and lung cancers.[187]

Epigenetics of HPV(+) HNSCC

Epigenetic changes play an important role in cancer development and progression. Just as with mutations or copy number changes, up-regulation of oncogenes or down-regulation of tumor suppressors via epigenetic changes can aid carcinogenesis. In cancer, epigenetic silencing of tumor suppressors through methylation occurs at least as frequently as mutations or deletions. Genome-wide gene expression profiling highlighted several hundred genes that are differentially expressed in HPV(+) and HPV(−) oropharyngeal cancers.[188] The majority of studies examining gene promoter methylation in

HNSCC are substantially descriptive without functional significance between methylation, gene expression, and clinical behavior. However, promoter hypermethylation of ALDH1A2, OSR2, GATA4, GRIA4, and IRX4—genes coding for proteins involved in retinoid metabolism—was found to correlate with decreased transcript expression, HPV gene expression, and improved survival.[189] Our findings indicated that SMG-1, a PI3K-related kinase family member, involved in the nonsense-mediated RNA decay process and maintenance of genome integrity, has low expression in HPV(+) OPSCC due to promoter hypermethylation, which may contribute to the enhanced radiation sensitivity of HPV(+) cells and tumors.[190] Interestingly, several genes from cadherin superfamily, including cadherins (CDH8, CDH13, CDH18, CDH19, CDH23) and protocadherins (PCDH10, PCDH15, PCDHB1, PCDHB4, and PCDHB15) that are all targets of polycomb repressive complex 2 and potential players in metastatic process, were selectively hypermethylated in HPV(+), but not in HPV(−) HNSCC.[191] In addition, higher DNA methylation in genic and LINE-1 regions, which most likely indicate a global hypermethylated phenotype, has been found in HPV(+) versus HPV(−) head and neck cancer cell lines.[52] However, recently it has become clear that the distinct gene expression and methylation signature of HPV(+) HNSCC (global hypermethylation) are found only in cancers harboring episomal HPV, whereas methylation and gene expression profiles of tumors with “integrated-only” HPV are very similar to HPV(−) tumors and normal tissue.[175] This finding hints at distinct carcinogenic mechanisms for cancers with integrated and nonintegrated HPV and heralds epigenetic changes as a major driver of cancer development in HNSCC with episomal HPV; however, more detailed and focused studies are needed to clarify this hypothesis.

Proteomics of HPV(+) and HPV(−) HNSCC

Gene expression and mutational analyses reveal clear differences between HPV(+) and HPV(−) HNSCC, but examining protein expression and activation has increased identification of pathways that are differentially activated based on HPV status. Comparing HPV(+) and HPV(−) tumors, proteomics studies have found differences in proteins primarily involved in metabolism, adhesion, differentiation, and keratinization.[192] However, the continued search for targetable signaling pathways prompted a recent

examination of protein and phosphoprotein expression, focusing on tumor-associated signaling cascades. Remarkably, 30% (41/127) of proteins or phosphoproteins involved in these pathways were differentially expressed.[24]

As expected, both cyclin D1 expression and Rb inhibitory phosphorylation were relatively increased in HPV(−) HNSCC compared to HPV(+) cancers. Differential expression and phosphorylation of these cell cycle genes is likely explained by HPV E7-dependent down-regulation of Rb, with resultant increased transcriptional activity of cell cycle driver E2F1. Consistent with previous reports, EGFR, STAT3, MYC, and insulin pathway proteins were also expressed at higher levels in HPV(−) HNSCC.[144,193,194] Surprisingly, HPV(−) HNSCC had increased activation of Akt as measured by phosphorylation of downstream targets.[24] Increased Akt activation in HPV(−) versus HPV(+) cancers was even more remarkable given the high percentage of HPV(+) cancers with activating mutations of PIK3CA and the absence of similar mutations in HPV(−) cancers. Together, these results suggest that both HPV(+) and HPV(−) HNSCC are dependent on Rb inhibition, albeit by different mechanisms. E2F1 amplification in HPV(+) tumors suggests that these tumors are particularly dependent on E2F1 activity. On the other hand, HPV(+) HNSCC seems to be less dependent on activation of RTK signaling compared to HPV(−) cancers.

Interestingly, high expression levels of several DNA repair proteins segregated to HPV(+) versus HPV(−) tumors. Additionally, elevated levels of apoptotic markers, including cleavage of caspases 3 and 7, were found in HPV(+) tumors. Finally, mechanistic studies revealed that activating mutations of PIK3CA in HPV(+) HNSCC preferentially stimulated mTOR, as opposed to the Akt pathway, suggesting that HPV(+) tumors rely on activation of PI3K, but not on downstream Akt activation.[24]

Treatment of HPV(+) HNSCC

Despite the dichotomous patient population, treatment response, and prognosis, and the fundamental molecular differences between HPV(+) and HPV(−) HNSCC, the presence of HPV alone does not currently play a role in treatment decisions. For advanced stage patients, treatment minimally includes platinum drugs concurrent with high doses of radiation. However, ongoing clinical trials are currently testing whether HPV(+) HNSCC may be

effectively treated with de-escalated therapy and less invasive surgery, in order to limit the serious side effects associated with traditional therapies.[195–197] In addition, cetuximab, an anti-EGFR antibody, which is currently used as a radiation sensitizer, is currently being investigated as another means of treatment de-escalation.[198]

Recent data that women vaccinated against HPV had a lower prevalence of oral HPV infection[199] suggest that both currently available HPV vaccines, Gardasil and Cervarix, protect against oral HPV infection and potentially HPV(+) HNSCC. Using a therapeutic HPV vaccine following the development of an infection or cancerous transformation in order to stimulate an immune response against cells harboring HPV and expressing HPV genes is another interesting area of scientific and clinical interest,[200,201] as are other immune-related therapies.[202]

The increasing knowledge of the molecular pathogenesis of HPV(+) HNSCC is driving discovery of newer, targeted, less toxic therapies. Several drugs, including demethylating agents, cyclin-dependent kinase inhibitors, mTOR inhibitors, WEE1 inhibitors, and PARP inhibitors, have been investigated in our laboratory and elsewhere. Many of these potential therapies have shown selective cytotoxicity for HPV-associated HNSCC in preclinical studies and thus represent acceptable candidates for clinical trials.

SUMMARY

The genetic and epigenetic alterations central to tumorigenesis of HNSCC are being uncovered with new technologies, building on prior knowledge in molecular biology. This chapter provides a framework for organizing and understanding the wealth of information being produced. Understanding the pathogenesis of HNSCC will be an essential foundation for discovery of new therapies. Importantly, it is becoming clear that HNSCC is not a single entity, but is rather a similar manifestation of a heterogeneous collection of etiologies and insults. Our approach to treatment of this cancer requires sophistication to match the complexity of the processes that were responsible for its creation.

Progress in advancing new targeted drugs has proven incremental and onerous since the relatively recent unlocking of the human genome, but many

new therapies are on the horizon (Table 2.4) and should allow us to treat HPV(+) and HPV(−) HNSCC in a more sophisticated, targeted, and personalized fashion. We are at the beginning of a journey to understand molecular defects that are drivers of HNSCC. As an indicator of progress in this venture, trials are already in place using molecular data to guide therapy. We are moving from relatively stagnant treatments based on histology, stage, and site to treatments based on individual defects in the tumor or the ability of the immune system to respond. As these therapies emerge, the next major advance will be in design and delivery of rational combinatorial therapies.

Table 2.4 Current Therapeutic Targets in HNSCC

Target	Functional Pathway	Drug Mechanism	Drug Name(s)	Stage(s) of Development
p53	DNA damage response, cell cycle/ apoptosis	Adenovirus gene therapy	Advexin	Phase 3
			ONYX-015	Approved in China
		Wee-1 inhibitors	MK-1775	Phase II
		Aurora kinase inhibitors	ZM447439, hesperadin, VX-680	Phase II
pRb	Cell cycle	CDK inhibitor	P276-00	Phase 2
EGFR	Growth signaling	Monoclonal antibody	Cetuximab	In clinical use
			Panitumumab, zalutumumab, nimotuzumab	Phase 2-3
Tyrosine kinases (EGFR, VEGFR, PDGFR, HER2, ErbB4, cKIT, RET)	Growth signaling	Tyrosine kinase inhibitors	Gefitinib, erlotinib, lapatinib, afatinib, sorafenib, sunitinib, vandetanib, pazopanib,axitinib, nilotinib	Phase 1-3
MEK	Growth signaling	MEK inhibitor	Trametinib	Phase 1
PI3K	Proliferation, resisting apoptosis	PI3K inhibitor	PX866, BKM120, BYL719, rigosertib	Phase 2
AKT	Proliferation, resisting apoptosis	AKT inhibitor	MK2206	Phase 2
mTOR	Proliferation, resisting apoptosis	mTOR inhibitor	Rapamycin, everolimus, temsirolimus, CC-115	Phase 1-2
JAK	Proliferation, resisting apoptosis	JAK inhibitor	Ruxolitinib	Phase 1
MET or MET/VEGFR	Angiogenesis, invasions/metastasis, proliferation	MET inhibitor or MET/VEGFR inhibitor	LY2801653, foretinib, E7050/ golvatinib	Phase 1-2
PDK	Cancer metabolism/ hypoxia	PDK inhibitor	Dichloroacetate	Phase 1
AMPK	Cancer metabolism	AMPK activator	Metformin	Phase 2

(Source: www.clinicaltrials.gov.)

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3 Pathology of the Head and Neck: Basic Considerations and New Concepts

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The role of the modern surgical pathologist is to identify tissue-based lesions and describe their known theranostic characteristics in order to accurately inform patient prognosis and clinical therapy. As such, the pathologist is an integral member of the multidisciplinary team responsible for the management of cancer of the head and neck. In the modern era, the creation of a pathologic diagnosis goes far beyond the straightforward “naming” of an entity based on histologic appearance, and may require close correlation with the gross specimen, clinical, radiographic, or molecular characteristics in order to evaluate and convey relevant information for appropriate patient care.

This chapter provides an overview of pathologic issues related to cancer of the head and neck and is divided into three sections. In the first, a general overview of the role of pathology in head and neck neoplasia is provided. “Histopathologic Parameters” section addresses histopathologic parameters evaluated by pathologists, with focus on those relevant in the assessment of mucosal squamous cell carcinoma. “Ancillary Studies (Pathologic Toolbox) and Applications” section provides an update of the diagnostic tools used by pathologists in routine clinical analysis, as well as a look at emerging technologies.

Basics of Pathology

Pathology Reporting

The pathology report provides the basis for all tissue-based clinical decisions. As such, it is a vital part of the patient's medical record. At the most basic level, the pathology report contains a description of the tissue examined by the pathologist, at both the gross and microscopic levels. If a lesion is present, the pathologist is responsible for establishing the general type of process (inflammatory, infectious, benign neoplastic, or malignant) and subclassifying it as specifically as possible with a name that conveys the lineage of the cells involved and the etiology of the process. In addition, adequate diagnosis of malignant tumors requires further specification as to cellular differentiation. Where evaluable, the extent of tumor is reported, including whether it is in situ or invasive, its size, presence or absence of vascular/lymphatic invasion, perineural invasion, or presence at surgical margins. Lymph nodes must be identified and examined for metastases and extranodal extension. Ancillary testing required for diagnosis or therapeutic applications may also be contained within the surgical pathology report.

The Surgical Pathology Specimen

Pathology specimens come in a variety of forms, ranging from cyst contents or solid tumor aspirations, to needle core biopsies and incisional or excisional biopsies, to radical, complex resections. Each specimen type must be properly labeled and promptly submitted to ensure that it is appropriately processed for subsequent evaluation. Pathologic examination begins with examination of the gross surgical specimen. Note is made as to the type of specimen, for example, biopsy (shave, core, punch, incisional, excisional), resection, or lymph node dissection, and the overall size.

Gross examination of biopsy specimens may be relatively simple. The tissue biopsied should be noted, if identifiable, as epithelial/mucosal, bone, cartilage, or soft tissue, and the specimen should be submitted entirely, with or without additional sectioning, depending on specimen size.

For excisions and resections consisting of large, complex specimens, as frequently results from head and neck resections, the gross examination may be more involved. The intricate anatomy of the head and neck requires the surgical pathologist to be aware of the normal structures and their relationships to one another, in order to properly assess tumor involvement. Correct orientation is key to the establishment of the status of the surgical margins and requires a close working relationship between the pathologist

and the surgeon. In many cases, surgeons can ensure proper orientation using sutures or ink to indicate critical margins. In complex cases, or those where nonmargin tissue has been disrupted, personal orientation of the pathologist to the specimen by the surgeon may be required.

After specimen orientation, the pathologist documents the structures present, sections the specimen, and records the size, appearance, and extent of the tumor. Sections submitted for histologic evaluation must represent areas requiring special attention, for example, surgical margins, lymph nodes, or bone invasion, that may impact the patient's prognosis and future management. Failure to properly evaluate and section the gross specimen can have significant adverse effects on patient care.

Subsequent to appropriate fixation of the specimen in formalin or other agents, the tissue is further mechanically processed, dehydrated, and infiltrated with paraffin. Depending on the type of tissue, the length of time needed for proper fixation varies; for instance, adipose tissue requires a longer processing time. Calcified specimens such as bones must be decalcified in acid or chelating agents prior to processing. Decalcification can take from hours to weeks, based on the specific agent used, the density of bone, and the thickness of the section. Processed tissue is embedded by hand into paraffin blocks, sectioned into 4- to 5-μm sections, and stained with hematoxylin and eosin (H&E) or other histochemical stain for routine histologic evaluation. Typically, specimen processing for routine formalin-fixed, paraffin-embedded (FFPE) tissues may take from a few hours to a day for small biopsies rapidly processed in specialized processors, to many days for complex bone resection specimens.

The surgical pathologist is completely dependent upon the tissue procured by the surgeon. Without appropriate or adequate material, an accurate diagnosis cannot be rendered. In general, biopsies should avoid necrotic tissues near the center of lesions. Transitional areas showing the interface between normal and abnormal tissue are preferred, such as the edge of an ulcer or the line of demarcation between a verrucous proliferation and flat epithelium. Superficial biopsies are rarely helpful; invasion of epithelial lesions cannot be determined without evaluation of the epithelial–stromal interface, in a full-thickness section. Failure to provide an adequate biopsy results in diagnostic and therapeutic delays as well as frustration for the patient, clinician, and pathologist alike. Repeat biopsies may be distorted by

postbiopsy inflammatory changes and degenerative artifact, further adding difficulty to appropriate interpretation.

It is also necessary to consider the differential diagnosis before placing biopsy tissue in fixative and sending it to pathology. Although in most circumstances, immediately placing tissue in fixative at the time of surgery is preferred, because tissues undergo ischemic changes and progressive autolysis the longer they remain unfixed, fresh tissue may be required by the pathology laboratory in certain circumstances. Ancillary studies such as flow cytometry or cytogenetics, which are frequently utilized in diagnosis of hematolymphoid proliferations, require fresh viable tissue, which must be sent directly from the operating room without delay for processing. Some laboratories may wish to save a portion of tissue in fixatives other than formalin for lymphoid biopsies for better preservation of cellular morphology.[1] If ancillary studies such as electron microscopy, molecular studies, or cytogenetics are anticipated, it is also recommended that fresh tissue be sent without transport delay and the pathologist be notified that special handling is required.

The use of frozen tissue biorepositories established from fresh tissue after minimal ischemic time is encouraged for preservation of neoplastic and uninvolved tissues. However, gross specimen dissection is best handled by the pathologist, and incision or sectioning of the specimen by the surgical team is discouraged, as it may create difficulties in appropriate pathologic evaluation of margins, or sectioning for microscopy.

Cytology

Cytologic preparations may be obtained from bodily site washings, cyst fluid aspirations, or solid tumor aspirations or may be made directly from the surgical specimen. Touch imprints, squash preparations, and scrape cytology specimens prepared from surgical specimens are commonly used as an adjunct technique to frozen section evaluation, particularly for evaluation of thyroid nodules, lesions of the central nervous system, or hematolymphoid lesions. Touch imprints are prepared by pressing a glass slide against the cut surface of tumor and are best used for lymphoid or hematopoietic processes, where cells easily transfer from tissue to glass. Squash preparation involves cutting minute portions of tumor (<1 mm^3) and pressing it between two slides to spread out cells. Squash preparations are best reserved for very soft tissues

that spread easily under pressure. To harvest cells for scrape preparations, a scalpel blade is used to scrape the cut surface of a lesion, and the material is then smeared onto a glass slide.

Fine needle aspiration (FNA) biopsies are performed by inserting a thin needle attached to a syringe into the mass of interest. Cells are harvested by using light suction applied to the syringe while the needle is rapidly moved back and forth through the tissue to loosen cells and obtain a sample from different regions. Material collected may be smeared directly on slides or saved in fluid for paraffin-embedded cell block preparation or for fluid-based cytologic preparations created using filtration or centrifugation. Smeared slides are rapidly fixed or allowed to air dry and stained for histologic evaluation with H&E, Papanicolaou stain, or Diff-Quick preparation. Additional unstained preparations can also be set aside for immunohistochemistry or molecular studies.

FNA is a reliable and safe method to obtain cytology specimens from cystic lesions, lymph nodes, and many types of solid tumors. Early concerns about nerve damage and biopsy tract seeding by tumor cells were largely unfounded,[2,3] with the most frequent complications being hematoma and infection. FNA biopsy is easily performed on palpable masses and may be used in conjunction with ultrasound imaging to improve accuracy and to target deep lesions.[4,5] Because it is relatively cost- and labor-effective when applied to the readily accessible structures of the head and neck, FNA biopsy has become the preferred screening diagnostic modality for clinically concerning neck masses, including lesions arising in the parotid, thyroid, or lateral neck. As with all techniques in medicine, FNA biopsy and interpretation is highly dependent on experience, with higher diagnostic accuracies reported by high-volume academic centers,[6] and improved rates of biopsy adequacy when performed or screened on-site for adequacy by cytopathologists.[7–10] FNA biopsy has proved invaluable in presurgical planning and patient counseling, particularly in regard to defining the need for procedures with higher risk of morbidity, such as nerve sacrifice or neck dissection.[11,12] FNA also allows for serial follow-up if a lesion continues to grow over time. Many surgeons do, however, prefer to verify cytologic diagnoses at the time of surgery with intraoperative frozen section (further discussed below).

Salivary Glands

Diagnosis of salivary gland neoplasms by FNA biopsy can be challenging. Many tumors are composed of a mixture of cell types, and even cytologically bland tumors can demonstrate an infiltrative growth pattern definitive for malignancy on final pathology.[13] Common sources of diagnostic error include cellular pleomorphic adenoma, low-grade carcinomas such as low-grade mucoepidermoid or papillary cystadenocarcinoma, lymphoepithelial cysts, and lymphoproliferative disorders.[14] Fortunately, the majority of tumors of the major salivary gland are benign, with pleomorphic adenoma and Warthin tumor representing the most common subtypes,[15] resulting in a high pretest probability of benign diagnoses. FNA biopsy of lesions of the major salivary glands has a high specificity for malignancy, with reported sensitivity, specificity, and accuracy for malignant diagnosis ranging from 73% to 92%, 94% to 100%, and 90% to 98%, respectively.[11,16–18]

Because FNA biopsy allows for the creation of cell block tissues, diagnostic accuracy may be improved by incorporating immunohistochemical or molecular analyses into final pathologic interpretation. In most instances, salivary tumors will undergo resection for definitive therapy, regardless of the FNA interpretation as benign or malignant. However, because FNA biopsy is largely comparable in accuracy to frozen section,[11,19,20] prior knowledge of the likely malignant potential enables the surgeon to better counsel the patients and prepare them in advance as to the necessity of wide resection, possibly including sacrifice of the facial nerve, or elective neck dissection. Discussions may also be entered into about postsurgical management and adjuvant therapy options, if required.

Neck Masses

It may be difficult to distinguish a benign from a malignant mass in the neck on the basis of clinical and radiographic information alone. Lesions may represent reactive lymphadenopathy, primary lymphomas, enlarging developmental cysts, infection (lymphadenitis), metastases to the lymph nodes, or benign or malignant mesenchymal tumors arising in soft tissue of the neck. Fortunately, ultrasound-guided FNA is one of the most accurate modalities for confirming the presence of metastatic disease in enlarged cervical nodes, with reported sensitivity for squamous cell carcinoma in solid

lymph nodes ranging from 80% to 90%.[21,22] FNA is less sensitive for malignancy in cystic neck masses, with sensitivity as low as 33%.[23,24]

Sensitivity and accuracy of FNA biopsy diagnosis of lymphoproliferative lesions is enhanced by concurrent immunocytochemistry, flow cytometry, and/or cytogenetic analyses. Dedicated FNA passes in addition to those needed for smear and cell block preparations may be required to obtain adequate material for these studies. In the absence of ancillary immunophenotyping studies or flow cytometry, the ability of FNA to correctly identify and classify lymphoma has been reported to be as low as 52%.[25] Immunocytochemistry increases accuracy to 70% and flow cytometry to 75% to 81%.[25,26] Flow cytometric analysis improves the ability to distinguish reactive lymphadenopathy from non-Hodgkin lymphoma, although it has little effect on identification of Hodgkin lymphoma. In other contemporary analyses, overall diagnostic accuracy of FNA biopsy of cervical lymphadenopathy reaches 82%,[27] with highest overall accuracy (up to 100%) reported for identification of metastatic carcinoma and lowest (~75%) for diagnosis of Hodgkin and non-Hodgkin lymphomas.[26,27] Sensitivity and specificity of FNA biopsy for lymphoma is user dependent, and some series have noted no benefit to FNA biopsy of cervical lymphadenopathy.[28] In the vast majority of cases, however, FNA biopsy interpretation by an experienced cytopathologist is an acceptable screening tool to triage management of a mass in the neck. Diagnoses of metastatic carcinoma in a cervical node appropriately trigger further evaluation to identify primary site or tumor-specific management protocols, while lesions concerning for lymphoma should undergo excisional biopsy for definitive diagnosis and subtyping. Benign or reactive lesions may be followed or rebiopsied depending on the level of clinical suspicion for malignancy.

Thyroid Lesions

Thyroid nodules are one of the most common indications for neck FNA. Palpable nodules are identified in ~5% of the adult population,[29,30] with between 20% and 75% of the population having clinically unrecognized nodules.[31,32] Reported incidence of thyroid carcinoma averages 5% in solitary nodules and 3% in multinodular goiter.[33] Presurgical diagnosis via FNA biopsy prevents unneeded surgery for benign, nonprogressive lesions

and helps to triage patients with a neoplasm for the appropriate procedure. Diagnostic accuracy of FNA biopsy of the thyroid is well established, with both specificity and sensitivity for malignancy of over 90% in large historical series.[34–37]

Standardization and interpretation of thyroid cytology has been greatly improved by the widespread adoption of systems such as the Bethesda reporting system, which classifies biopsies in a 6-tiered system as: Bethesda Class 1—nondiagnostic or unsatisfactory, Bethesda Class 2—benign, Bethesda Class 3—atypia of uncertain significance or follicular lesion of uncertain significance, Bethesda Class 4—follicular neoplasm or suspicious for follicular neoplasm, Bethesda Class 5—suspicious for malignancy, and Bethesda Class 6—malignant (Table 3.1).[38–40]

Table 3.1 Bethesda Classification of Thyroid Cytology

Bethesda Classification	Frequency of Diagnosis	Risk of Malignancy	Recommended Management
1. Nondiagnostic, Unsatisfactory	<15%	N/A	Repeat FNA with ultrasound guidance
2. Benign	30%–75%	<2%	Clinical follow-up
3. Atypia of undetermined significance, Follicular lesion of uncertain significance	<10%	20%–40%	Repeat FNA
4. Follicular neoplasm, Suspicious for follicular neoplasm	~5%	40%	Lobectomy
5. Suspicious for malignancy	<5%	70%	Thyroidectomy or lobectomy
6. Malignant	~5%	>95%	Thyroidectomy

Nondiagnostic biopsies occur in 3% to 14% of thyroid FNA,[41,42] with higher percentages resulting from procedures performed by less experienced clinicians in the absence of immediate pathologic assessment of adequacy and a lower incidence when performed and assessed in FNA clinics by trained cytopathologists.[8,9,43] Ultrasound guidance further increases diagnostic success rates for difficult-to-palpate nodules.[43] Benign lesions, for example, nodular hyperplasia or chronic thyroiditis, are identified on cytology in approximately 30% to 70% of aspirated nodules,[41,44] with reported false-negative rates as low as 0% to 2%.[44,45]

The most challenging cases to manage are those diagnosed as Bethesda 3, as final diagnosis may range from benign nodular hyperplasia to papillary or follicular thyroid carcinoma. Initially, lesions with atypia of uncertain significance were predicted to run a 5% to 15% risk of malignancy.[38] In

practice, studies have reported malignancy rates ranging from 20% to 38%, not including incidentally discovered second lesions in the resected specimen.[41,42,46] Moreover, the Bethesda category 3 is intended to account for no more than 10% of cases in a given practice.[38] Overusage of the category can lead to additional management dilemmas. Although the Bethesda guidelines recommend repeat FNA for indeterminate lesions, and studies have shown that 40% to 50% of indeterminate lesions can be classified as benign on repeat FNA,[42,46] other consensus guidelines recommend surgery as the next step.[47] Triage of cytologically indeterminate lesions to reflex mutational analysis or commercial propriety gene expression analyses to more clearly delineate benign from malignant based on molecular signature has become increasing popular and is discussed in greater detail in “Ancillary Studies (Pathologic Toolbox) and Applications” section.

Lesions diagnosed as suspicious for follicular neoplasm on resection are found to be hyperplasias, adenomas, follicular carcinomas, and less frequently, papillary carcinoma, with malignancy rates of up to 40% to 46%.[45], [48] Determination of malignancy in an encapsulated follicular nodule requires identification of capsular or vascular invasion, features for which neither FNA nor frozen section is sensitive. Thus, appropriate management for Bethesda 4 lesions is lobectomy with evaluation of the entire capsule of the lesion on paraffin section. Oncocytic or “Hürthle cell” features are seen in nonneoplastic conditions as well as both benign and malignant neoplasms and have little diagnostic significance when reported on FNA.[49,50]

Approximately 70% of thyroid nodules reported as suspicious for malignancy on FNA (Bethesda 5) turn out to be malignant after definitive excision,[48] and the vast majority of these are papillary thyroid carcinoma (PTC), whereas >95% of lesions with cytologic diagnosis of malignancy are confirmed after resection.[51,52]

FNA biopsy of the thyroid does elicit biopsy site changes in the thyroid gland, including hemorrhage, necrosis, cystic degeneration, fibrosis, inflammation, and nuclear cytologic atypia of adjacent tumor cells as well as squamous or oncocytic metaplasia. Capsular disruption by biopsy tract and subsequent entrapment of follicular cells may simulate capsular invasion. Such changes may be mistaken as evidence of malignancy on subsequent FNA biopsy or resection[53–55] and must be interpreted with caution in

postbiopsy resection specimens.

Orbit

FNA is sometimes used to diagnose deep unresectable posterior orbital tumors or those for which access would require large, complex craniofacial surgery. Reported success rate (defined as being diagnostically helpful or accurate) approached 80% in older studies,[56,57] with the majority of lesions being lymphoproliferative or inflammatory conditions. FNA is rarely used in this location, due to the rarity of orbital masses and the technical skill required for the procedure. In the modern era, endoscopic surgery with direct visualization of the lesion is preferred to procure tissue for histopathologic evaluation.[58,59] FNA has also been proposed as a diagnostic tool for uveal melanomas and other intraocular tumors,[60,61] with sensitivity and specificity for malignancy reported as 100% and 98%, respectively. Complications include intraocular hemorrhage and rarely retinal detachment or tumor seeding.[62]

Intraoperative Consultation (Frozen Section)

During the course of surgery, it may be necessary to send a specimen for immediate pathologic examination, to help guide surgical decision making. Intraoperative consultation may take the form of gross specimen examination; cytologic preparations, as discussed above; or frozen section. Specimens may also be sent to the frozen section laboratory for rapid processing for biorepository or for tissue harvesting for cytogenetics, microbiology studies, flow cytometry, diagnostic mutational screening, or gene expression assays. Because the frozen section laboratory works in a time-sensitive fashion and may have multiple cases waiting for results before surgery may proceed, “curiosity frozens,” the result of which will not affect the procedure under way, but which may cause harm to the diagnostic material or delay other waiting cases, are strongly discouraged. It must be clearly understood that the frozen section interpretation is a preliminary diagnosis, intended only to provide immediate actionable information to the surgeons at the time of surgery, and is not meant to be the basis for postsurgical treatment or patient management. Decisions about adjuvant therapy must therefore be deferred until a definitive final diagnosis is rendered on FFPE tissues.

Appropriate uses of intraoperative consultation include establishing biopsy adequacy, triage of tissue for ancillary studies such as flow cytometry, or to make a preliminary diagnosis that will affect the extent of surgery. Margins are evaluated for adequacy of clearance, and additional margins may be sent until tumor clearance is achieved. Specimens may also be sent for tissue confirmation, such as confirmation of parathyroid glands in need of preservation during thyroidectomy.

Frozen section analysis requires that tissue be rapidly examined at the gross level, oriented, and inked if indicated and sections cut for histologic analysis. These tissue sections are embedded in gel matrix and rapidly frozen at –20°C to –30°C. Thin, 4- to 7-μm sections are cut using a microtome, and the tissue is stained with H&E for evaluation. Different tissues have varying water and lipid contents causing them to freeze at different rates, which may lead to tissue and cellular distortion. Sectioning frozen tissue may be technically difficult, particularly for adipose or dense fibrous tissue, and may not produce satisfactory sections for interpretation. Heavily calcified tissues, such as bone, often cannot be sectioned at all. Air-drying artifact may also be introduced if sections are not fixed rapidly enough after being cut. Some tumors, in particular melanocytic lesions, should not be sent for frozen evaluation, as frozen artifact precludes sufficiently accurate identification of malignant cells.

Due to the above technical limitations of the technique combined with the rapid turnaround time required (within 20 minutes from receipt as recommended by the College of American Pathologists), frozen section may be less accurate than paraffin sections. Reported overall error rates for frozen section vary, based on both specimen type and experience. In large studies of general surgical cases, accuracy of frozen section reaches 98%, with deferral rates of 2% to 3%.[63–65] Overall, historical concordance rates are similar for head and neck surgeries,[66,67] which are among the services most heavily reliant on intraoperative consultation.[65] Discrepancy rates on surgical margins are much higher than those for any other specimen type[68–72] and are further discussed below.

In addition to specimen-, technical-, and sampling-related errors, frozen section "errors" also include misinterpretation or miscommunication of results.[73] Read-back verification by the surgeon is required to ensure proper diagnosis communication between the interpreting pathologist and treating

surgeon.[74]

Margins

Negative surgical resection margins with complete clearance of malignancy are required for local cancer control.[75] Margins are therefore frequently sent for frozen section during the course of resection of mucosal squamous cell carcinomas and may be a point of controversy for both pathologists and surgeons. Factors impacting on proper evaluation of margins include the type and complexity of surgical specimen, orientation of the specimen, adequate sectioning and gross evaluation, and correct interpretation of histologic findings. Despite best efforts, all frozen section diagnoses carry the risk that permanent section will reveal tumor not diagnosed at the time of frozen section. In general, accuracy of frozen section in the diagnosis of margins ranges from 89% to 99%,[76–78] with specificity >95%, but low sensitivity. Many groups report that approximately half of the cases with positive final margins were not identified on frozen (range of missed positive margins, 15% to 83%).[68–72,77] False-negative margins on frozen section most frequently result from sampling error, in which carcinoma is absent on the frozen section slide but is found on permanent sections after deeper sectioning.[76] False negatives also occur when the area sampled on frozen section did not truly represent the closest extent of tumor to margin.[68,79] Less frequently, false negatives result from diagnostic misinterpretation of tissue present on the slide, a source of error that may depend on the specimen type, case volume, degree of experience with head and neck tumor evaluation by involved surgical pathologists, and presence of altered tissue states after adjuvant therapy. Frozen section evaluation of margins is particularly problematic in tumors that have been previously irradiated.[69,77]

Historically, the value of frozen section margin evaluation in improving survival was based on the observation that patients with negative margins at the time of frozen section had local recurrence rates of 14%, compared with 20% in patients who required additional supplementary margins to be taken for clearance and 80% in patients for whom adequate clearance was not achievable.[75]

Some authors have questioned the value of frozen section evaluation on local disease control and survival.[69,70,80] Gerber et al.[68] recently reported

that, in a retrospective series of 178 patients undergoing primary resection of oral cavity squamous cell carcinomas with curative intent, frozen section was performed in 111 patients, with positive final margins in 20% of cases, compared with 28% of those who did not undergo intraoperative consult. This difference was not statistically significant.[68] DiNardo and coauthors[69] had similar results and suggested that, after taking into account both accuracy and cost-effectiveness, frozen section evaluation was best used judiciously and largely reserved for patients in whom subsequent margin revision would have the highest chance of success. Effect of frozen section on margin status is also dependent on other factors, such as tumor size,[68] site,[67] and the skill of both the surgeon and the pathologist. Studies have reported widely varying rates of positive margins on final pathology, from between 4% and 53%,[71,72,81–87] suggesting that individual institutions should establish their own quality assurance parameters for when to perform margin frozen section and how those results should affect patient management.

Diagnosis

Masses of every conceivable anatomic site pass through the frozen section laboratory for intraoperative diagnosis on a regular basis. In the head and neck, salivary tumors, thyroid nodules, parathyroid lesions, lymph nodes, and mucosal biopsies form the bulk of this material. FNA has made inroads in diminishing the use of frozen section diagnosis in many of these lesions, but some surgeons prefer a cautious approach with review of tissue-based diagnostic material prior to embarking upon an aggressive surgical procedure.

Frozen section has been reported to have sensitivity and specificity as high as 98.5% and 99%, respectively, for diagnosis of malignant lesions of the parotid, although it is less accurate at distinguishing between different types of benign or malignant tumor.[88–90] Frozen section can also distinguish true salivary gland processes from metastatic tumor in periparotid lymph nodes and can triage lymphoid proliferations to appropriate ancillary studies. Compared to cytology, frozen section is reported to have a lower false-negative rate for detection of salivary gland malignancy.[91]

Thyroid lesions are frequently sent for frozen section to confirm malignant diagnoses made on FNA or to attempt a definitive diagnosis of

lesions with indeterminate or suspicious cytology. Not all such frozen sections are appropriate. FNA diagnosis of PTC (Bethesda 6) has a <5% false-positive rate,[92–94] and frozen section is not warranted prior to proceeding with total thyroidectomy. Likewise, frozen section of nodules with a benign diagnosis on FNA is unwarranted[95–97] and provides no additional diagnostic information unless a clinically suspicious second nodule that was not previously biopsied is detected during the course of the operation. Frozen section is insensitive for malignancy in tumors with an FNA diagnosis of "follicular neoplasm," which may include hyperplasia, follicular adenoma, non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), follicular carcinoma, or follicular variant of papillary carcinoma in the differential diagnosis.[98,99] Follicular carcinoma requires identification of vascular and/or capsular invasion for diagnosis, features that are often focal and unlikely to be serendipitously present on frozen section, whereas the follicular variant of papillary carcinoma may present with subtle nuclear features that cannot be recognized in frozen tissue.[100,101] Frozen section has a variable sensitivity of 17% to 70% and specificity of 100% in malignant diagnosis of follicular pattern neoplasms, but a deferral rate of over 50%.[102–107]

Frozen section, in conjunction with intraoperative touch or scrape preparations, is best used to evaluate lesions diagnosed as atypical or suspicious for malignancy and can usually detect PTC; medullary carcinoma, poorly differentiated; and anaplastic carcinoma, among other malignancies, with an 84% sensitivity for malignancy, 100% specificity, and 57% likelihood of diagnosing PTC in cases with a preoperative diagnosis of Bethesda 5 lesion.[93,108] Cytologic preparations are recommended as an adjunct study to better examine nuclear details for characteristic features of PTC. It is estimated that frozen section consultation alters the surgical procedure in <1% of cases with preoperative benign diagnosis on FNA,[96] ~5% of those with follicular diagnosis,[109] and 20% to 57% of those with cytologically suspicious diagnosis.[96,110]

Although lymphoid proliferations are rarely diagnosed on frozen section, frozen section of lymph nodes is valuable in intraoperative diagnosis of lymph nodes metastases[111] and has been suggested as a methodology for sentinel lymph node evaluation in squamous cell carcinomas of the head and

neck[112] (discussed in greater detail in “Histopathologic Parameters” section below).

Histopathologic Parameters

Tissue lesions can be characterized by a number of different parameters. At the most basic level, histologic review determines if the sampled tissue is normal or atypical. Atypical conditions include reactive, inflammatory, and neoplastic conditions among others. For neoplastic lesions, one critical distinction is benign or malignant. However, classifying a tumor simply as malignant conveys insufficient prognostic and therapeutic information. To this end, the art of pathology has developed multiple systems of tumor classification and subclassification to more precisely delineate behavior.

Tumor Classification

Lineage

Tumors are typically classified based on the histologic line of differentiation (commonly referred to as the cell of origin) as epithelial, mesenchymal, hematopoietic/lymphoid, or neural/neuroectodermal. Within lineage, there exists a myriad of more specific subtypes, which can generally be identified based on histologic, immunophenotypic, and/or molecular characteristics. By far, the most common malignant tumors affecting the head and neck arise from mucosal or glandular epithelium. Non–glandular-derived epithelial malignancies are carcinomas, with squamous cell carcinoma being the most common subtype. Gland-forming epithelial malignancies are adenocarcinomas. Malignant mesenchymal tumors are termed sarcomas, whereas lymphoproliferative malignancies are lymphomas. Neuroectodermal structures give rise to a variety of benign and malignant tumors, including melanoma, olfactory neuroblastomas, malignant peripheral nerve sheath tumors, and others.

Squamous Cell Carcinoma.

Squamous cell carcinoma is the single most common type of carcinoma affecting the head and neck. Tumors arise within stratified squamous

epithelium, both cutaneous and mucosal, including oral cavity, pharynx, larynx, and nasal cavity. Squamous cell carcinoma may be further classified into conventional type or as one of several uncommon subtypes, each with its own distinctive clinicopathologic characteristics and behaviors (Table 3.2).

Table 3.2 Classification of Squamous Cell Carcinoma Variants of the Head and Neck

Conventional squamous cell carcinoma
Keratinizing
Nonkeratinizing (frequently HPV associated)
Variants
Acantholytic
Adenosquamous
Basaloid
Spindle cell
Verrucous
Nasopharyngeal carcinoma
Basaloid
Keratinizing
Nonkeratinizing (EBV-associated)
Differentiated
Undifferentiated
Sinonasal undifferentiated carcinoma
NUT midline carcinoma

EBV, Epstein-Barr virus; HPV, human papillomavirus.

Within the category of conventional squamous cell carcinoma, a further distinction is made between keratinizing and nonkeratinizing or hybrid tumors (Table 3.3).[113–117] Keratinizing squamous cell carcinomas historically represent the bulk of squamous cell carcinomas arising in the oral cavity and larynx and are associated with a history of alcohol consumption,

smoking, or chronic epithelial inflammatory conditions. Histologically, keratinizing squamous cell carcinomas are characterized by stratified malignant epithelium with distinct cell borders and intercellular bridging. Keratinization may be represented as cytoplasmic eosinophilia in more poorly differentiated cases or more typically by the presence of anucleate keratinocytes or "pearl" formation in well-differentiated tumors (Fig. 3.1). Keratinizing squamous cell carcinomas are, in general, highly aggressive, and advanced disease responds poorly to therapy.[118,119] Five-year survival rates depend on TNM stage and site and vary from up to 85% for glottic tumors to ~50% for supraglottic, hypopharyngeal, or buccal tumors.[119,120]

Table 3.3 Distinction Between HPV-Positive and HPV-Negative Squamous Cell Carcinoma

	HPV Positive	HPV Negative
Age	<60 y	>60 y
Gender	M > F	M > F
Site	Oropharynx (lingual and palatine tonsils)	All mucosal sites of oral cavity, pharynx, larynx, nasal cavity
Risk factors	Number of sexual partners, Immunosuppression	Tobacco, alcohol, chronic inflammatory conditions
Histology	Nonkeratinizing	Keratinizing
P16 expression	Positive (strong nuclear and cytoplasmic expression in >70% of cells)	Negative to patchy weak expression
Stage at presentation	Early metastasis with small primary tumor (pT1N2)	Larger primary tumor, but later metastasis. (pT1-2, N0-1)
Morphology of metastases	Cystic	Solid
Prognosis	5-year survival 70%–80%	5-year survival 25%–85%

HPV, human papillomavirus.

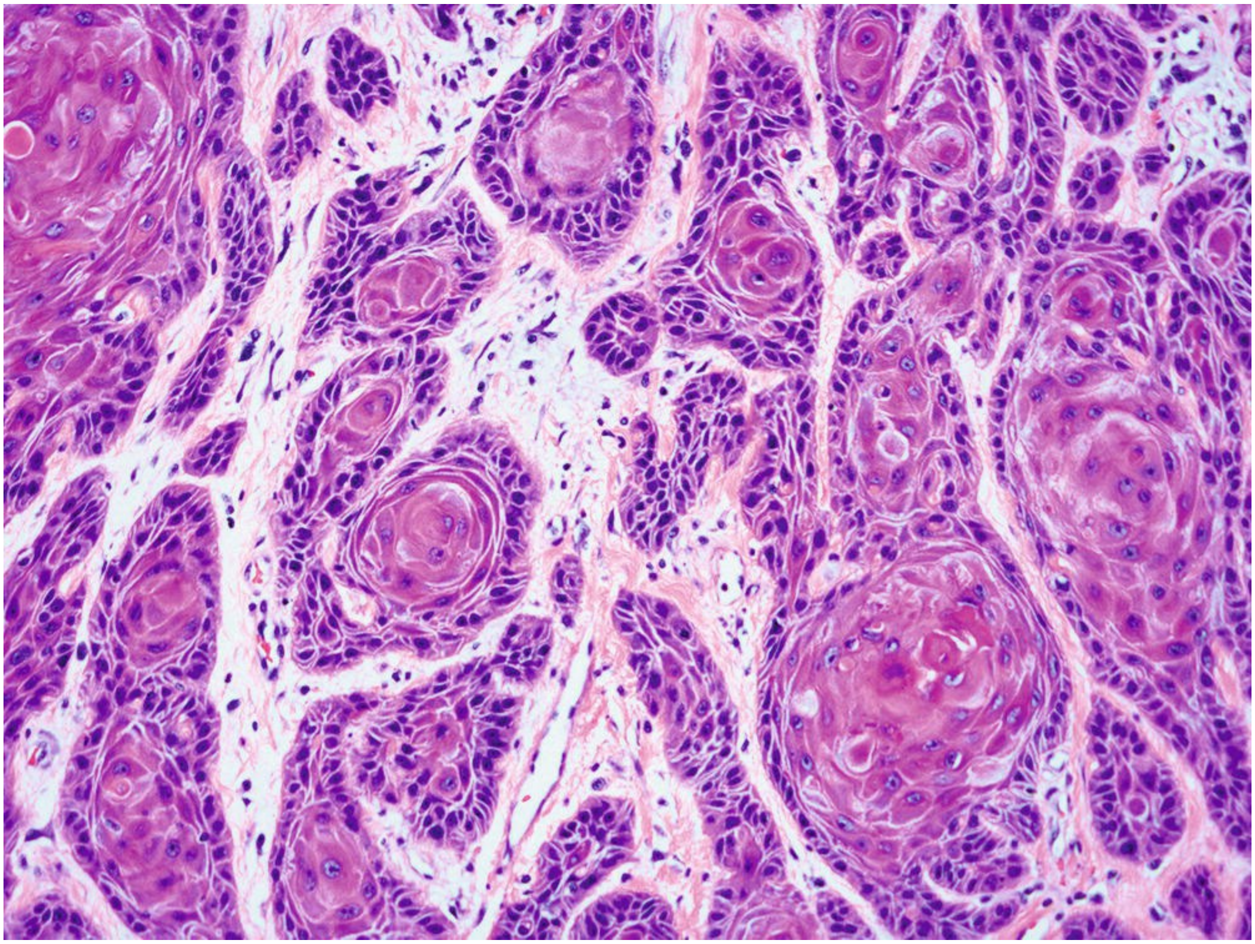
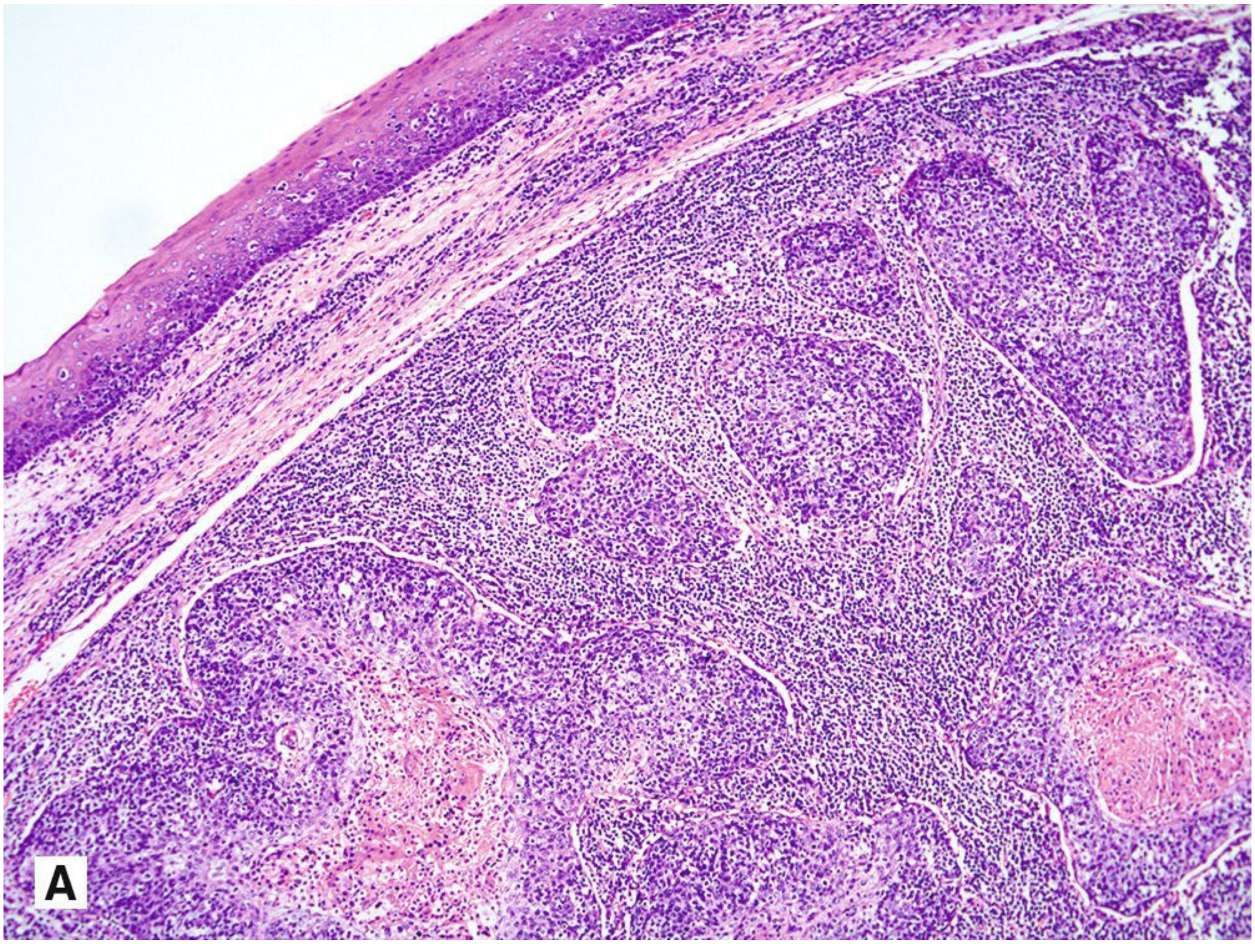
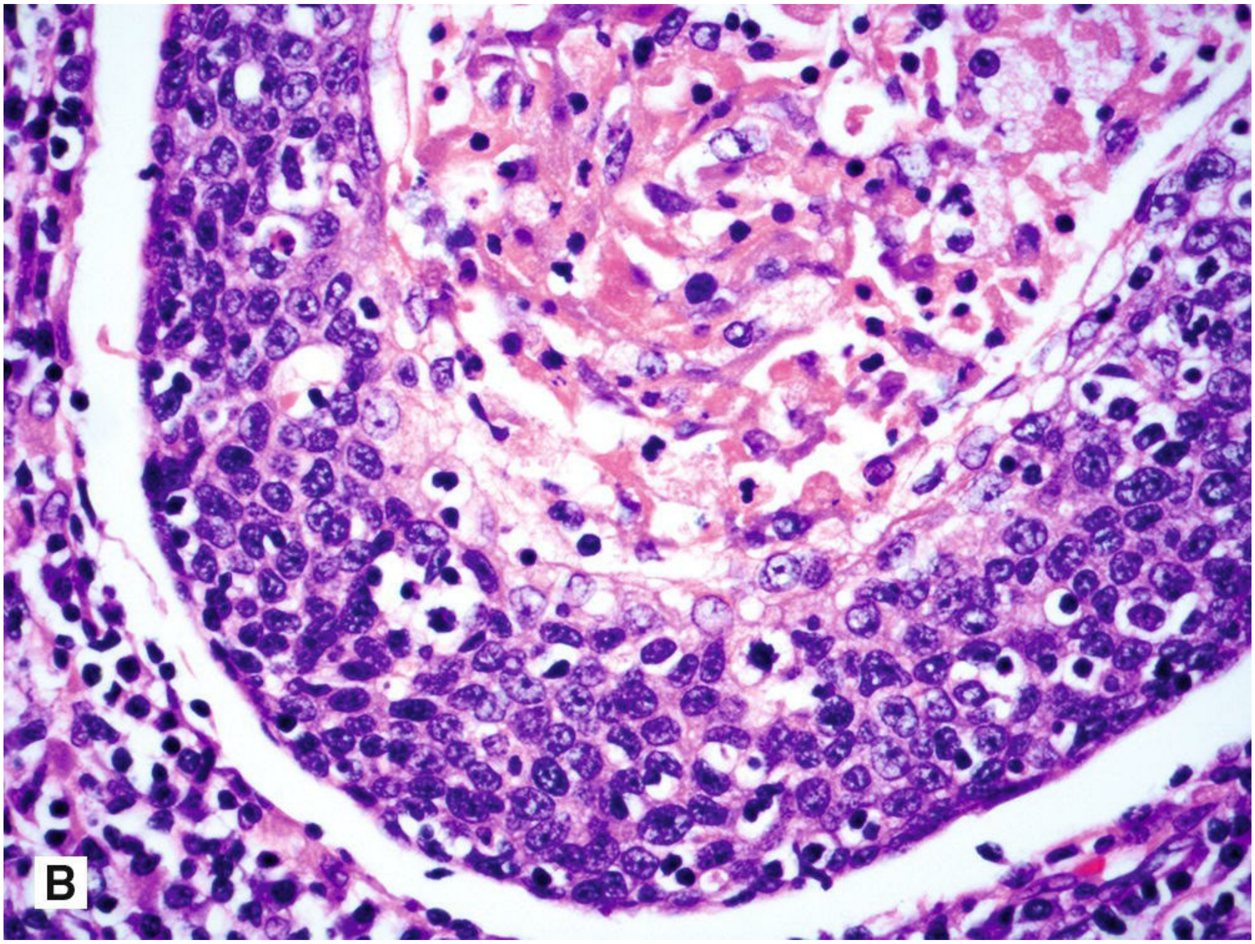


Figure 3.1 Invasive keratinizing squamous cell carcinoma characterized by cells with prominent cytoplasmic eosinophilia (keratinization) and clear spaces in between cells (intercellular bridging).

Nonkeratinizing and hybrid (focally keratinizing) squamous cell carcinomas are characterized by the complete/near absence of keratinization or by the admixture of nonkeratinizing and keratinizing cells, respectively. These tumors arise nearly exclusively in the oropharynx in association with tonsillar crypt epithelium and are most often associated with infection by high-risk human papillomavirus (HPV) genotypes, mainly HPV16, 33, 35 or 18 (Fig. 3.2).[121,122] As keratinizing squamous cell carcinomas have shown declining incidence in the past decade with decreased smoking prevalence, the proportion of HPV-associated carcinomas has increased.[123–125] These tumors possess a distinctive pathophysiology, with early lymph node metastasis, but superior outcomes compared to conventional squamous cell carcinoma, even in advanced disease.[113,126,127] Five-year relative survival rates are estimated

to be ~75% compared to 24% to 40% for non–HPV-associated oropharyngeal cancers.[128]

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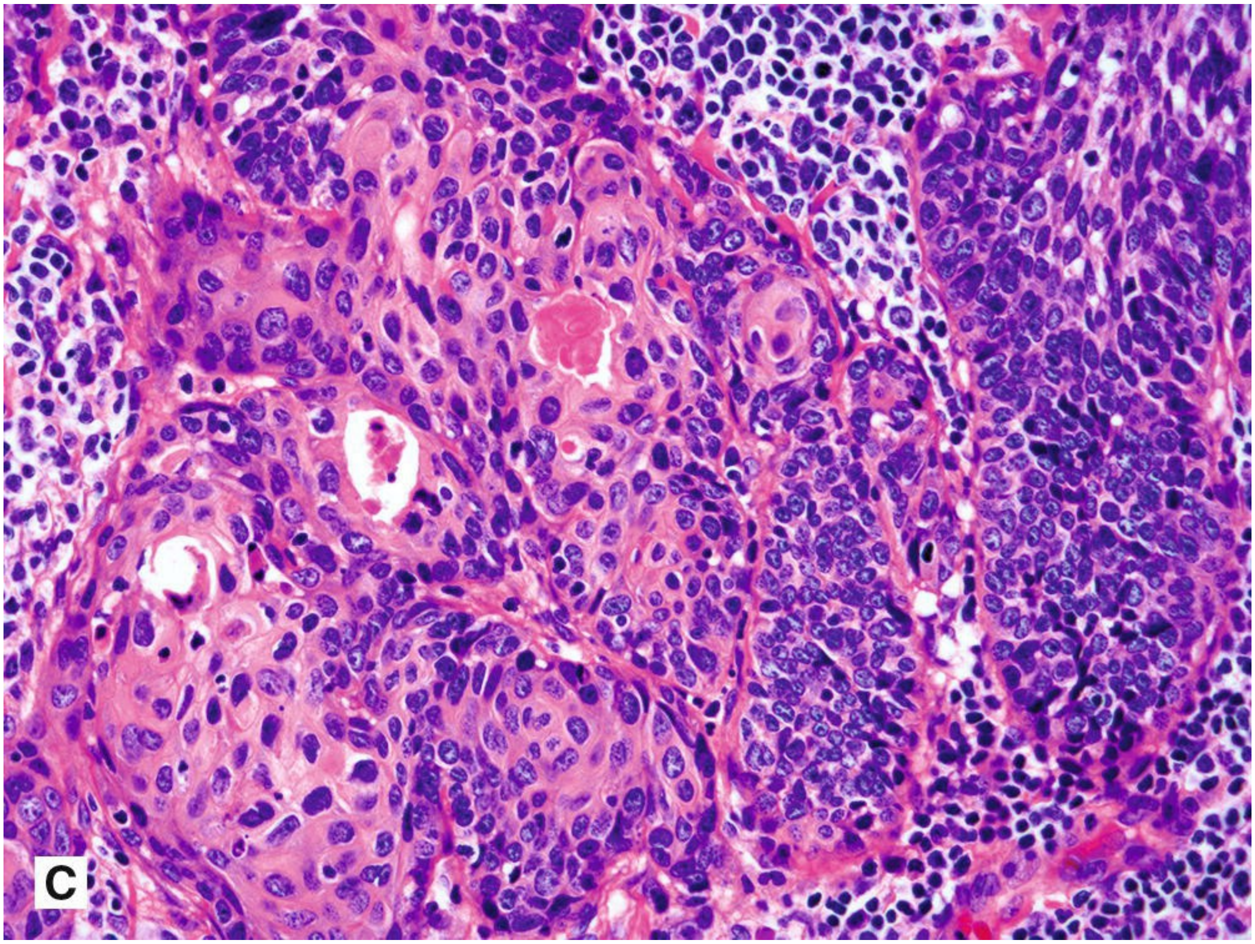
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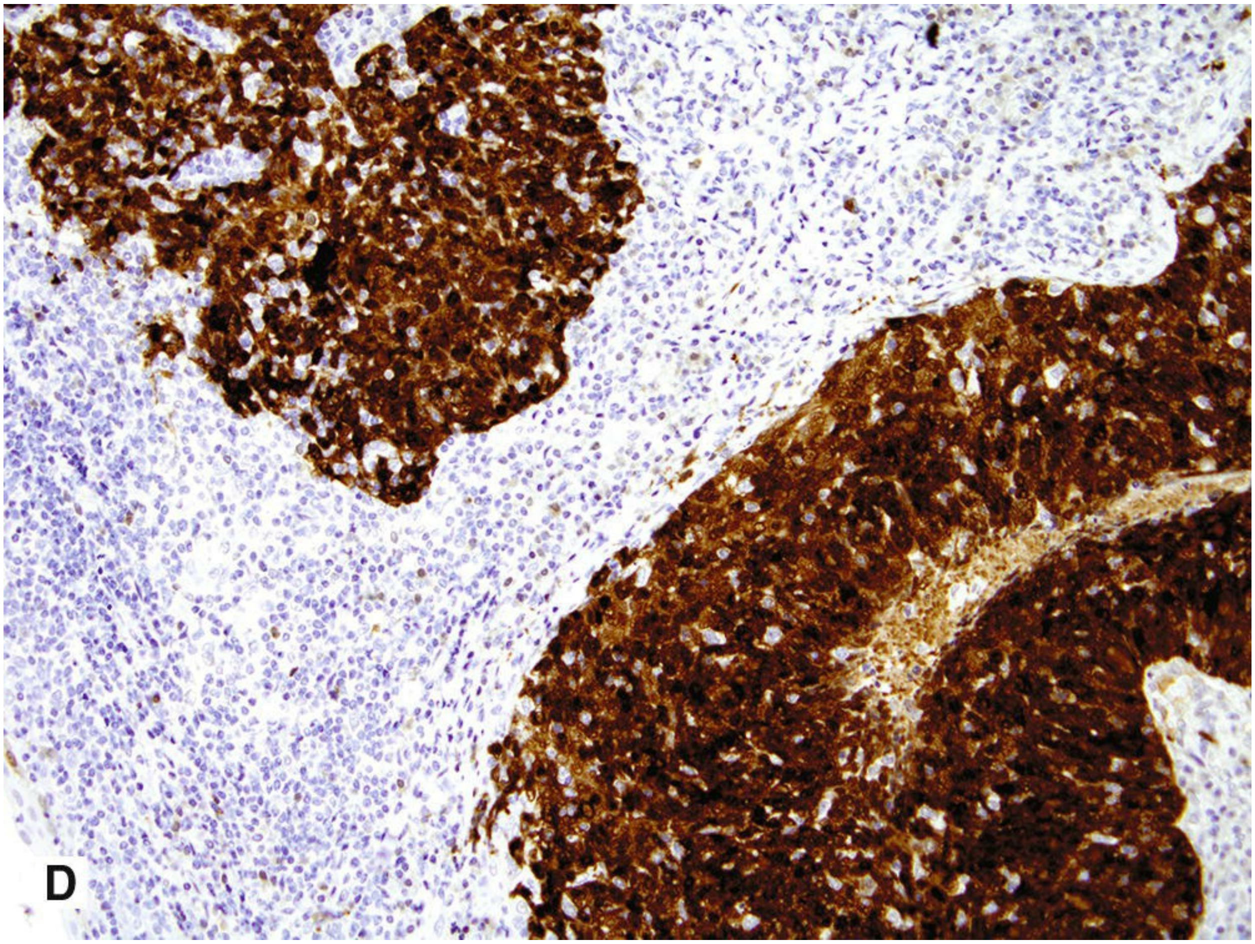


Figure 3.2 Oropharyngeal HPV-associated carcinoma. **A:** Low magnification of a submucosal infiltrative solid and cystic neoplasm. **A:** At higher magnification, the lesional cells are devoid of keratinization (i.e., nonkeratinizing). **C:** Hybrid carcinoma showing an admixture of nonkeratinizing and keratinizing malignant cells. **D:** Diffuse and strong p16 immunoreactivity (nuclear and cytoplasmic) represents a surrogate marker for HPV16 confirms the neoplasm as HPV associated; reflex in situ hybridization and PCR analysis identified the presence of high-risk HPV (not shown).

Nonkeratinizing squamous cell carcinoma often presents with neck metastasis and clinically occult primary lesion. Deep biopsy of lingual and pharyngeal tonsils or tonsillectomy may be required to locate the primary tumor, as microscopic tumors often arise deep within tonsillar crypts and are not detectable by superficial biopsy.[129] Nonkeratinizing tumors are variously described as having “immature,” “transitional,” “basaloid,” or “poorly

differentiated" histologic features, although they are now thought to represent relatively well-differentiated tumors recapitulating the phenotype of tonsillar crypt epithelium. Tumors characteristically express strong and diffuse nuclear and cytoplasmic p16 protein as a side effect of oncogenic viral protein inhibition of RB-mediated cell cycle arrest.[130] The presence of p16 immunoreactivity in a cervical nodal metastasis without a known primary cancer is strongly correlated to an oropharyngeal primary cancer.

Basaloid squamous cell carcinoma was initially described as a highly aggressive subset of squamous cell carcinoma that occurred in older males with a peak incidence from 60 to 80 years and showed malignant differentiation toward a phenotype similar to that of basal cells.[131] Basaloid squamous cell carcinoma may arise in a variety of mucosal sites in the upper aerodigestive tract including the larynx, hypopharynx, oropharynx, and sinonasal tract. Irrespective of site of origin, the histologic findings are similar, and tumors are characterized by multilobular, nested growth pattern with frequent comedonecrosis, foci of abrupt keratinization, and stromal hyalinization (Fig. 3.3). The overlying mucosa shows only limited foci of intraepithelial dysplasia. Unfortunately, nonkeratinizing, HPV-associated carcinomas have a similar-appearing cellular differentiation, and the term basaloid squamous cell carcinoma has been subverted by many authors to include both the highly aggressive "true" HPV-negative basaloid squamous cell carcinomas and the less aggressive nonkeratinizing HPV-associated variant.[132,133] Communication between pathologist and treating clinician is essential to ensure that the appropriate prognostic information is conveyed. When in doubt, HPV testing is essential.[132,133]

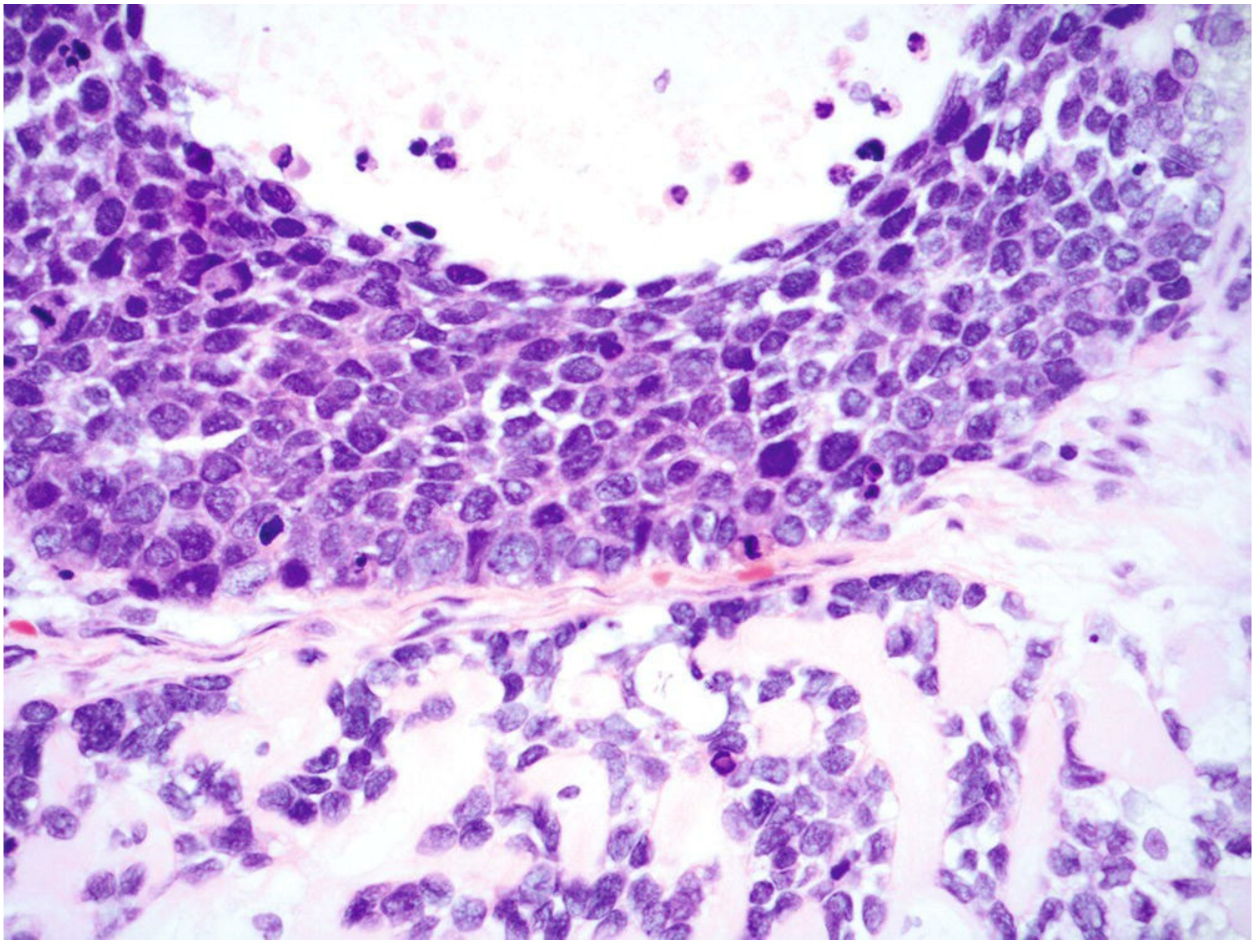


Figure 3.3 Basaloid squamous cell carcinoma composed of cells with hyperchromatic nuclei (basaloid cells), nuclear pleomorphism, and increased mitotic activity. The tumor nests include comedo-type necrosis **(top)** and associated stromal hyalinization **(bottom)** resembling the reduplicated basement membrane seen in salivary gland neoplasms. In areas not shown, there was evidence of squamous differentiation. This tumor was HPV negative.

Verrucous squamous cell carcinoma is a locally aggressive variant most commonly arising in the oral cavity of older patients and characterized by a markedly hyperplastic, filiform, warty architecture, and a broad, pushing invasive growth pattern (Fig. 3.4).[134,135] These tumors may be extremely difficult to diagnose on biopsy, as the large cell size and abundant keratinizing cytoplasm often make nuclear enlargement difficult to appreciate. Moreover, invasion is difficult to assess in the absence of infiltration. Proper diagnosis therefore relies on an adequate biopsy specimen.

Biopsy is best taken from the edge of the lesion to show the interface between tumor and normal mucosa and should be deep enough to reach underlying submucosa. Pure verrucous carcinomas do not exhibit any infiltrative growth and do not metastasize. The presence of infiltrative nests, "hybrid verrucous carcinoma," is associated with behavior akin to conventional squamous cell carcinomas. Verrucous carcinomas are associated with chronic inflammation and usage of smokeless tobacco.[136] Tumors may cause extensive local morbidity if left untreated, but in general, prognosis is good, with 5-year survival rates reported from 80% to 95%.[118,136]

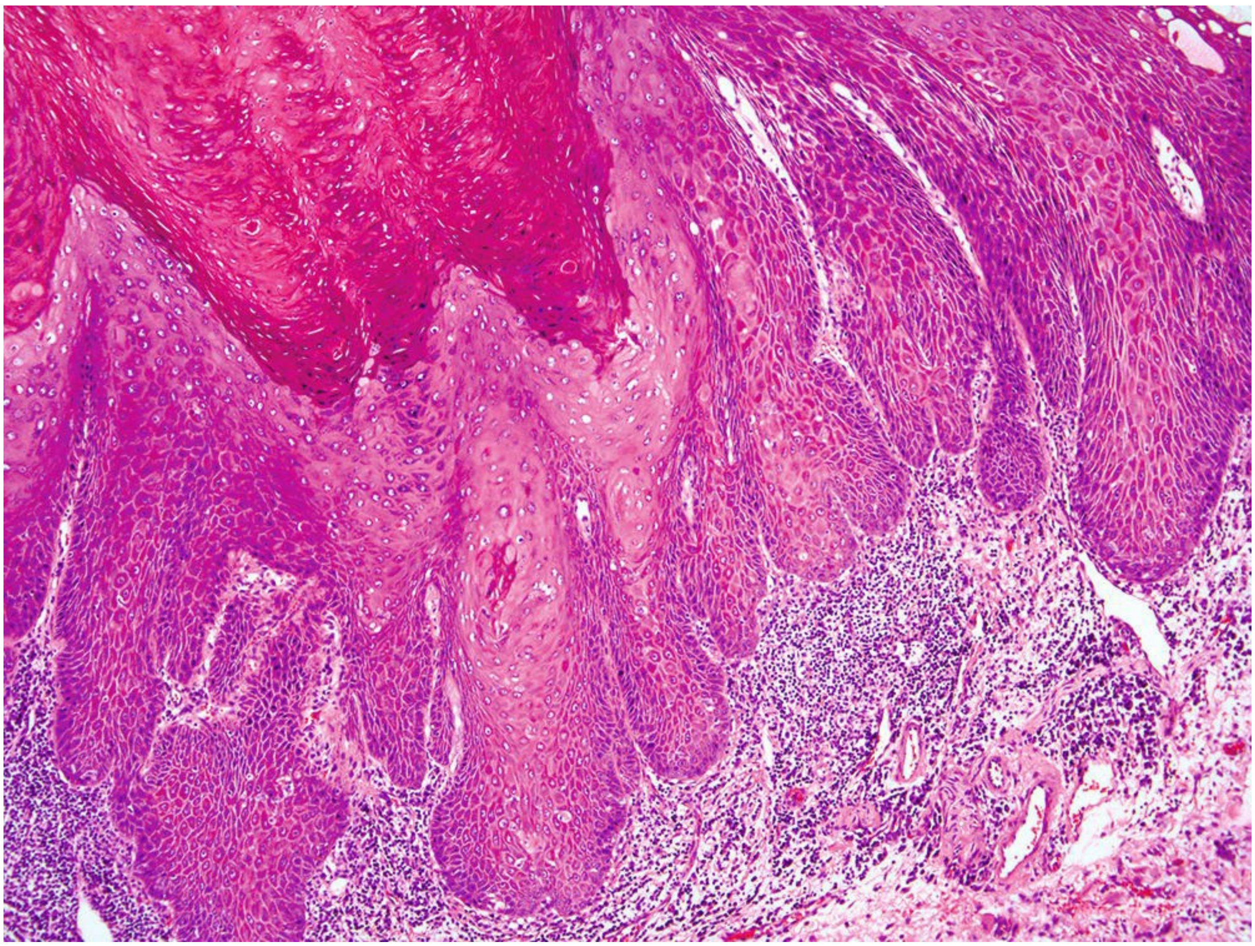
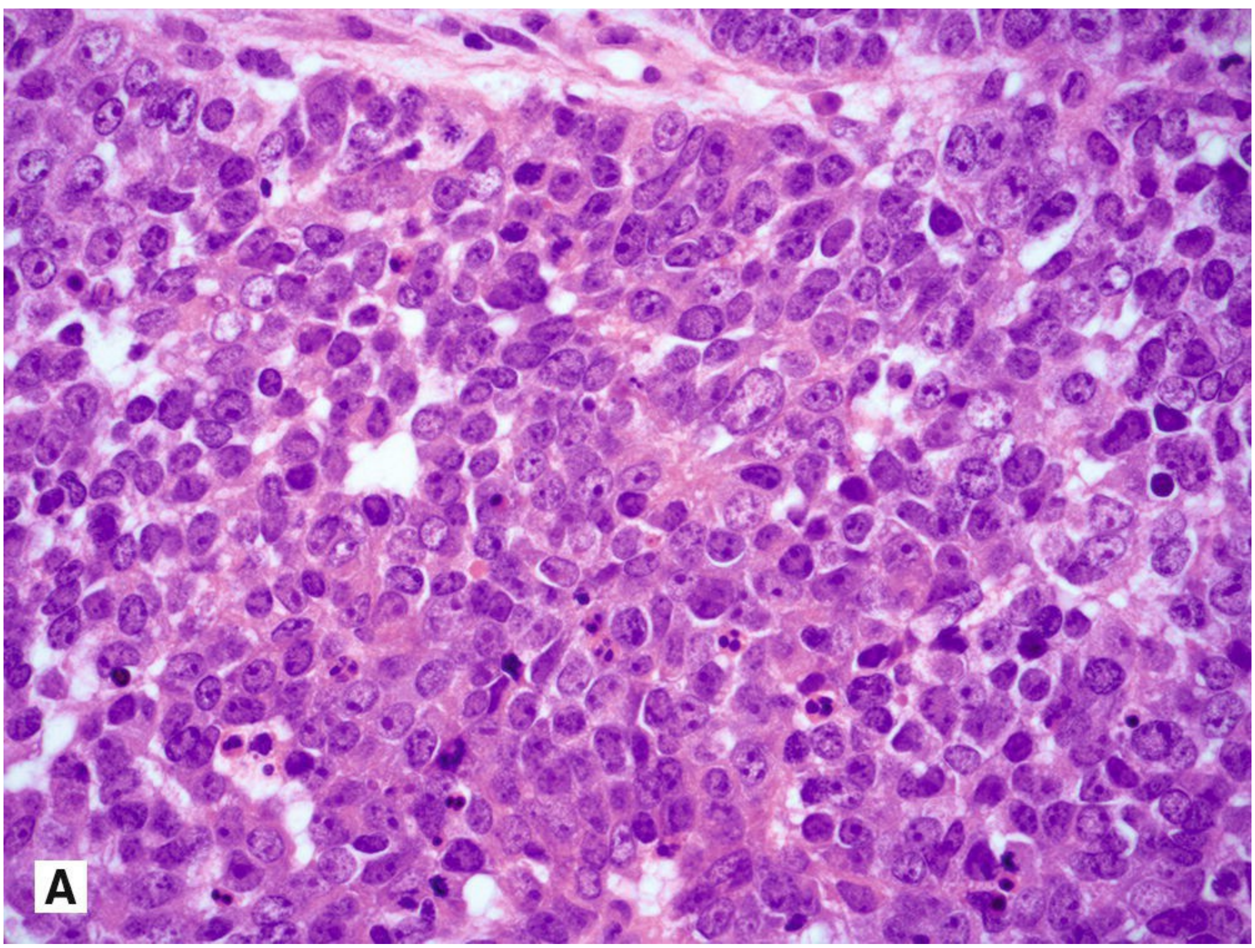


Figure 3.4 Verrucous carcinoma characterized by (tiered) keratosis of the surface and a bland epithelial proliferation with downward extending rete ridges (so-called pushing margin) and absence of epithelial dysplasia.

Sinonasal Undifferentiated Carcinoma.

Sinonasal undifferentiated carcinoma (SNUC) is a rare, aggressive

malignancy characterized by rapid local spread. Tumors are composed of nests, sheets, and trabeculae of malignant, poorly differentiated cells with scant cytoplasm, large nuclei, and, typically, prominent nucleoli (Fig. 3.5). Mitotic rate is high, and necrosis is frequently abundant. Malignant cells may express simple keratins and rarely neuroendocrine markers.[137] The etiology of SNUC is unclear; tumors are negative for Epstein-Barr virus (EBV) and HPV. Because of their rapid onset and extensive local involvement at presentation, SNUC have poor prognosis. The major differential diagnoses for SNUC include (in no particular order) rhabdomyosarcoma, olfactory neuroblastoma, nasopharyngeal undifferentiated carcinoma, small cell neuroendocrine carcinoma, poorly differentiated squamous cell carcinoma, and NUT midline carcinoma among others (Table 3.4). When the diagnosis is in question, correlation with the clinical and radiographic features is critical to making the correct diagnosis. Successful treatment is dependent on radical resection in conjunction with adjunct chemoradiation.[137]



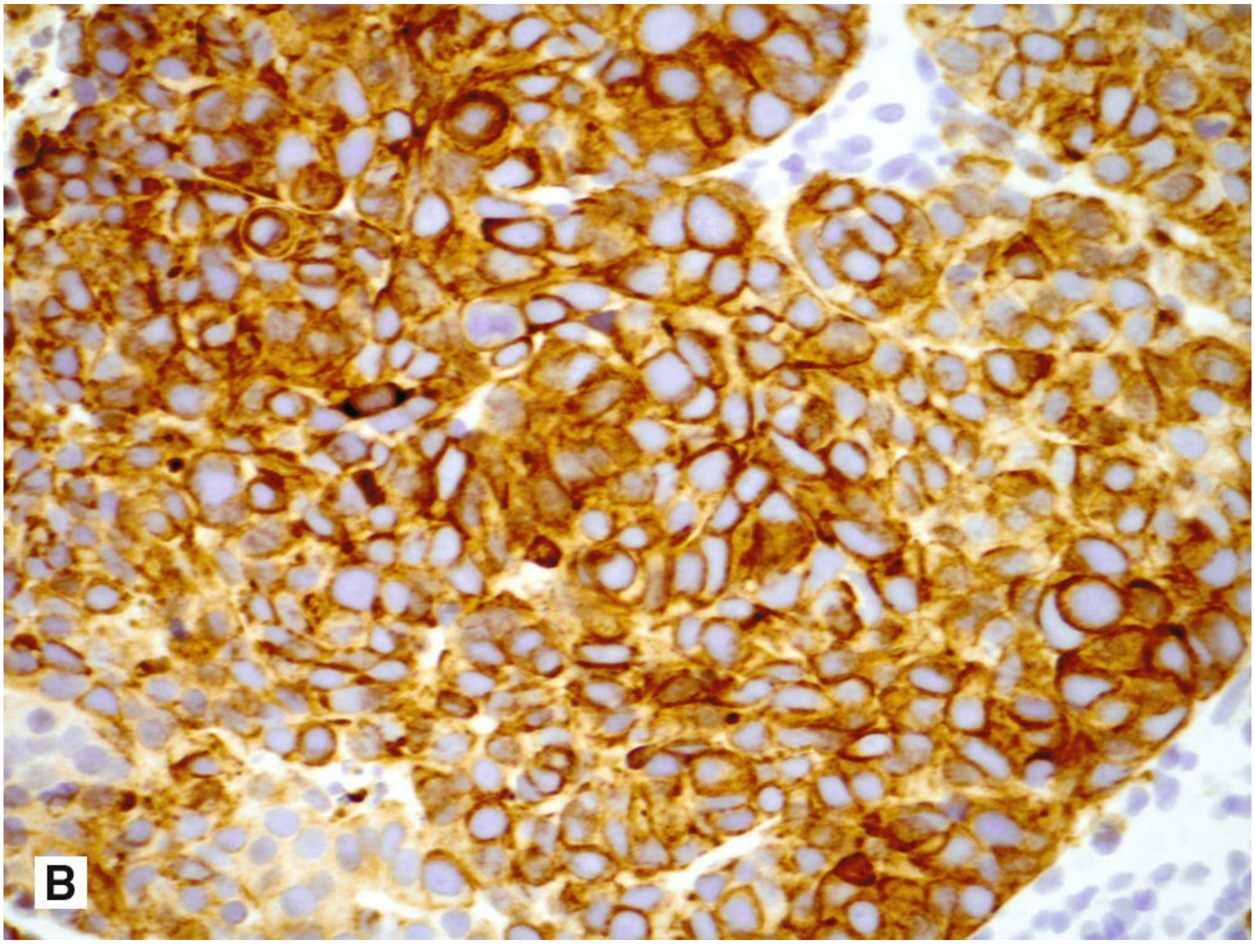


Figure 3.5 Sinonasal undifferentiated carcinoma (SNUC). **A:** Sinonasal high-grade malignant neoplasm characterized by cells with large nuclei, prominent nucleoli, scant cytoplasm, and increased mitotic activity lacking evidence of cellular differentiation. **B:** Cytokeratin (CAM5.2) immunoreactivity confirms the neoplasm as being of epithelial cell origin and in the absence of immunoreactivity indicative of any other tumor type as well as absence of EBV, the clinical findings, and location of the tumor coupled with the light microscopic findings would be diagnostic for SNUC.

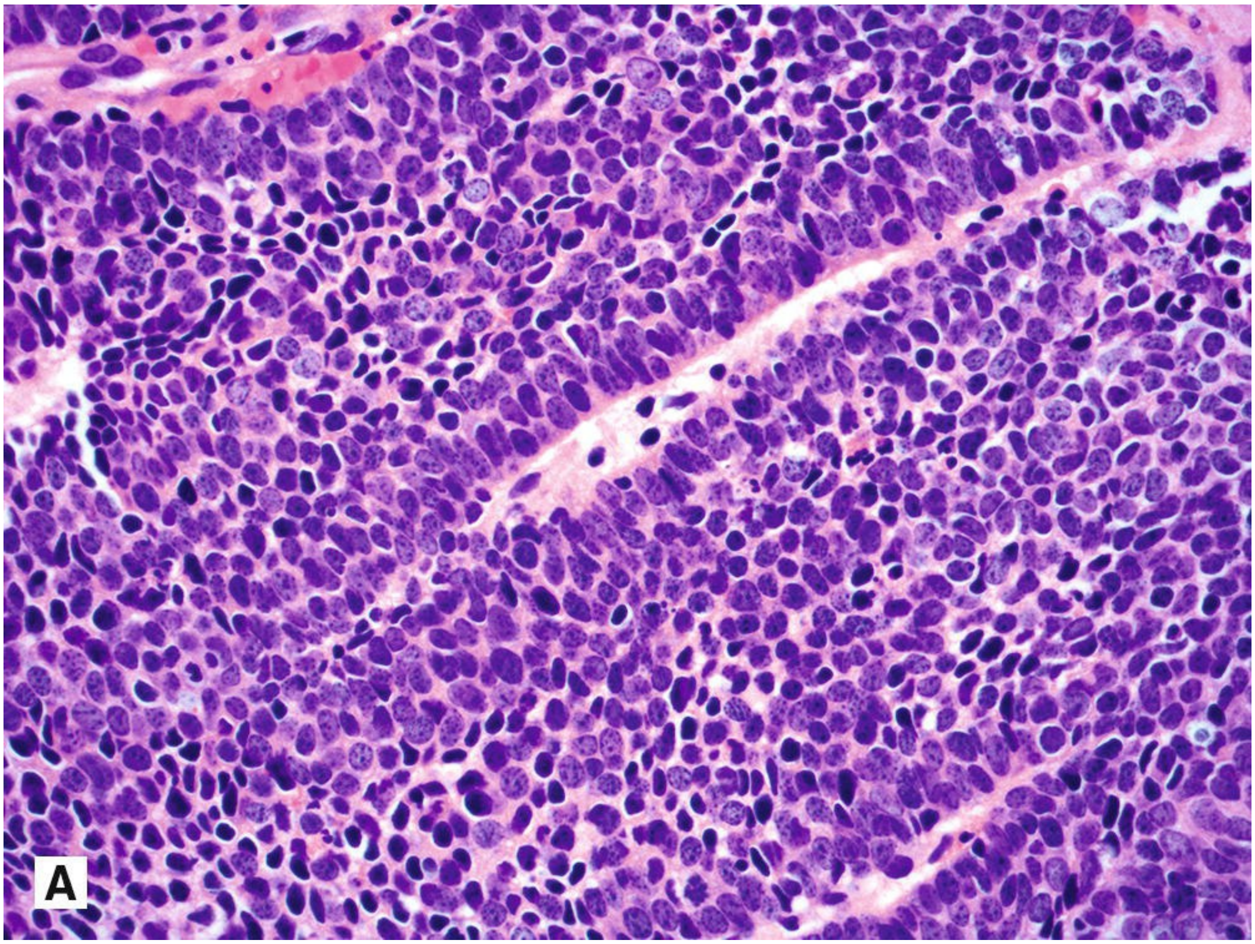
Table 3.4 Small Round Cell Malignant Tumors of the Sinonasal Tract

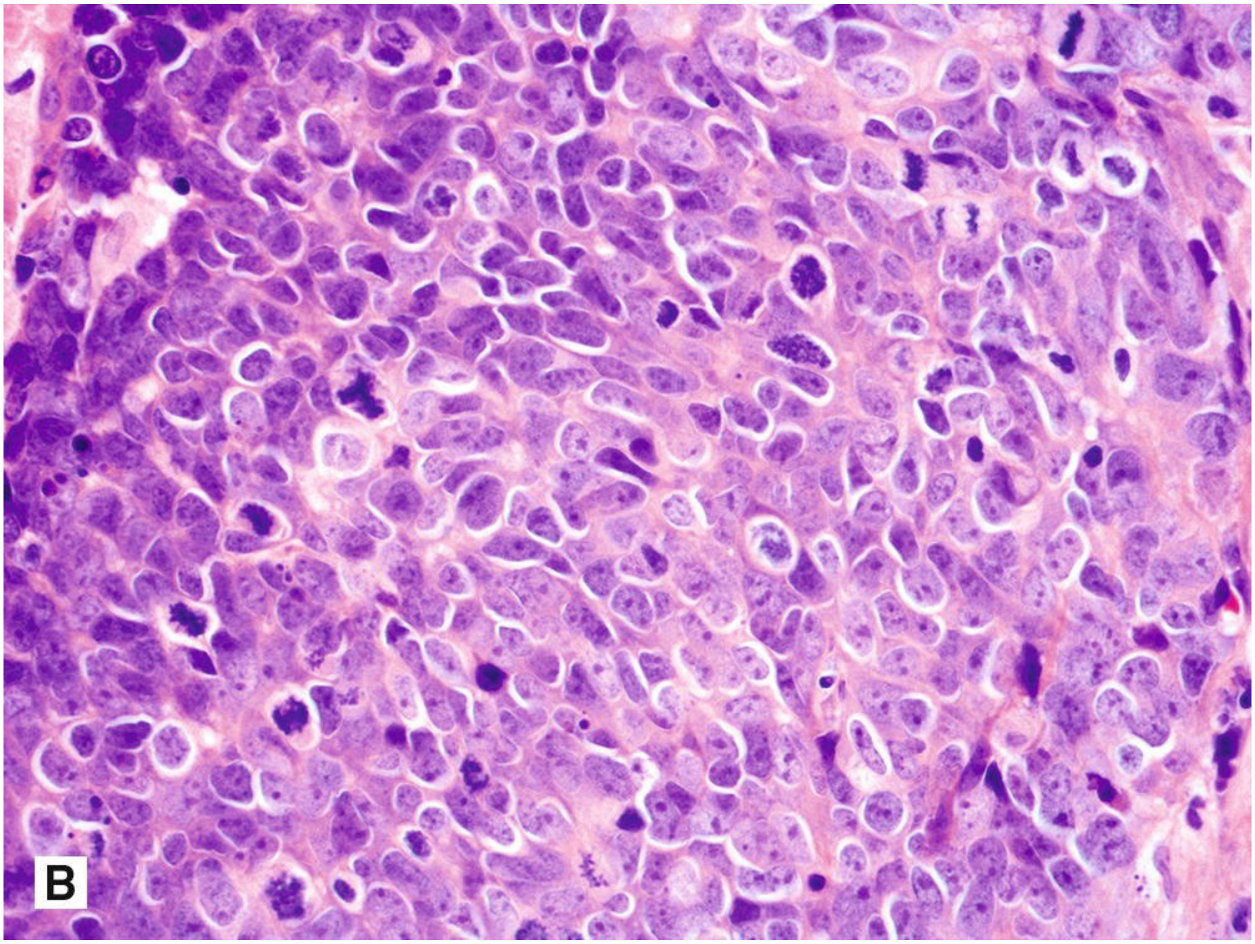
Epithelial
Neuroendocrine carcinomas
NUT midline carcinoma
Sinonasal undifferentiated carcinoma
SMARCB1 (INI-1)-deficient carcinoma of the sinonasal tract
Mesenchymal
Ewing family of tumors (Ewing sarcoma/primitive neuroectodermal tumor)
Rhabdomyosarcoma
Alveolar
Embryonal
Neuroectodermal
Melanoma
Olfactory neuroblastoma
Hematolymphoid
Lymphomas (i.e., NK/T cell lymphoma, nasal type)

Nasopharyngeal Carcinoma.

Nasopharyngeal carcinoma (NPC) represents a phenotypic spectrum of squamous cell carcinoma types, including keratinizing, nonkeratinizing, and basaloid morphologies. The nonkeratinizing type is most common and accounts for 75% of all cases of NPC. Nonkeratinizing NPC typically occurs in adults, with peak incidence between 40 and 60 years, and is two to three times more common in men than women. Tumors tend to have extensive local spread, early lymph node metastases, and the propensity for hematogenous metastases.[138] Nonkeratinizing NPC is subdivided into two morphologic types including differentiated (15% of all NPC) and undifferentiated (60% of all NPC). The differentiated subtype of nonkeratinizing NPC (formerly referred to as lymphoepithelioma) is characterized by the presence of stratification of malignant cells with well-defined borders (Fig. 3.6), whereas the undifferentiated subtype of NPC (NPUC) shows a syncytial growth pattern with crowding of cells and large,

vesicular nuclei with prominent nucleoli (Fig. 3.6). In some cases, the malignant cells may be spindle shaped. Clinically, there is no relevance to the distinction between differentiated and undifferentiated NPC. Both types are characterized by an associated nonneoplastic (benign) lymphoid proliferation that may overrun and obscure the malignant cells, resulting in the so-called lymphoepithelial morphology with tumor cells arrayed in plexiform nests interrupted by aggregates of nonneoplastic lymphocytes.

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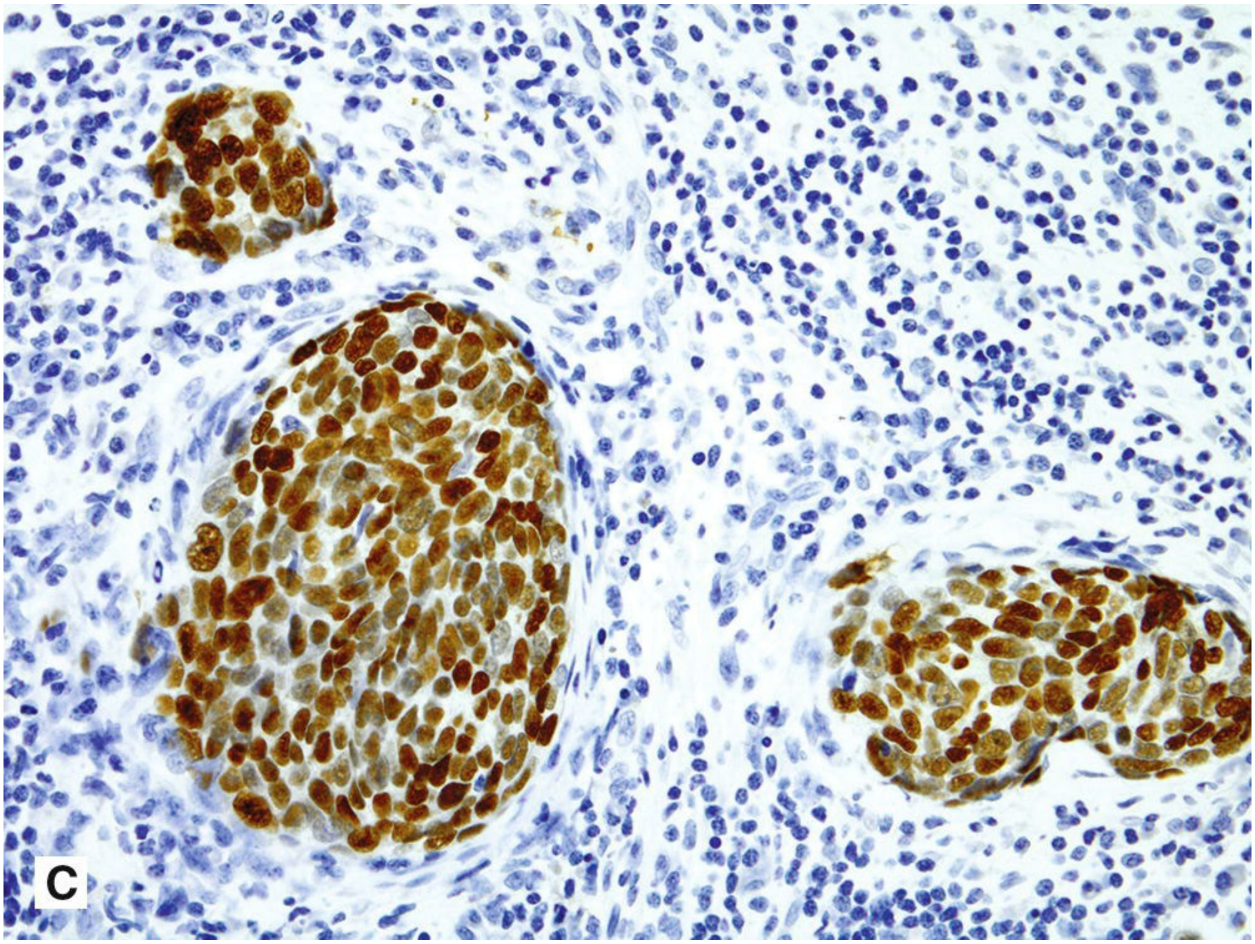


Figure 3.6 Nasopharyngeal carcinoma, nonkeratinizing types. **A:** Differentiated type characterized by cohesive cords, stratification of malignant cells with well-defined borders. **B:** Undifferentiated type shows syncytial growth pattern with crowded cells and large vesicular nuclei with prominent nucleoli. **C:** In situ hybridization for Epstein-Barr–encoded RNA (EBER) is diffusely positive (nuclear staining). Both subtypes of nasopharyngeal carcinoma, nonkeratinizing types, are associated with EBV.

Nonkeratinizing NPCs are frequently associated with Epstein-Barr virus (EBV), and the presence of diffuse (nuclear) positivity for Epstein-Barr encoded RNA (EBER) by in situ hybridization (ISH) is diagnostic (Fig. 3.6).[138] NPC is more common in regions where EBV is endemic (e.g., China) and is rare in the United States.[138] It is critical to make the distinction between nasopharyngeal nonkeratinizing carcinoma (associated with EBV) and oropharyngeal nonkeratinizing carcinoma (associated with HPV) as the behavior and prognosis are different, although both result from viral

infections. Another potential diagnostic dilemma given overlapping histologic features and presence of cytokeratin immunoreactivity includes differentiating NPC from SNUC. The presence or absence of EBV will allow the distinction between these tumors with NPC associated with EBV and SNUC negative for EBV. Keratinizing and basaloid NPC behave similarly to their counterparts arising elsewhere in the upper aerodigestive tract.

Of note, the use of the designation viral-associated carcinoma for NPC (EBV-associated) and oropharyngeal carcinoma (HPV-associated) may be adopted in future classifications of head and neck neoplasm.

NUT Midline Carcinoma.

NUT midline carcinoma is a rare, aggressive malignancy defined by chromosomal rearrangements, most commonly between 15q14 and 19p13.1, resulting in fusion of the *NUT* gene locus to *BRDU4* or *BRDU3*, among other partners, and subsequent overexpression of NUT protein.[139,140] Although NUT midline carcinoma may arise anywhere in the body, the majority of reported cases arise in the upper respiratory tract and mediastinum.[139] Histologically, NUT midline carcinomas appear poorly differentiated and may or may not exhibit evidence of squamous differentiation in the form of abrupt keratinization. The presence of immunoreactivity for NUT protein marker (nuclear staining) confirms the diagnosis. In the sinonasal tract, NUT carcinomas are thought to be frequently misdiagnosed as squamous cell carcinoma or SNUC. The distinction is important because NUT midline carcinomas may present at any age and have an average survival of less than a year.[139]

Carcinoma of the Salivary Glands.

Salivary gland carcinomas are rare, with reported incidence annual rates in the United States of only 1.3/100,000 individuals. The parotid gland is the most common site and accounts for up to 80% of cases, followed by the minor salivary glands, submandibular gland, and sublingual gland. Most malignant tumors arise in the superficial lobe of the parotid gland. The likelihood of a salivary gland tumor to be malignant also varies by site. Carcinoma is identified in <30% of parotid tumors, 40% of submandibular gland tumors, 50% of minor salivary gland tumors, and up to 90% of sublingual masses.[141]

Diagnosis of salivary gland neoplasia is made more complex by the number of described types of carcinoma, with over 20 malignant salivary gland carcinomas recognized (Table 3.5). The most common primary salivary gland malignancies, each accounting for 10% to 25% of cases, are mucoepidermoid carcinoma and adenoid cystic carcinoma (Figs. 3.7 and 3.8), with specific incidence rates showing geographic variation.[142,143] Precise histologic diagnosis of salivary gland tumors can be difficult, as many tumors are composed of a mixture of cell types or may show a spectrum of morphologic phenotypes. As a result, adenocarcinoma not otherwise specified (NOS) accounts for ~10% of cases.[142]

Table 3.5 Classification of Salivary Gland Carcinoma

Acinic cell carcinoma
Adenoid cystic carcinoma
Adenocarcinoma, NOS
Adenosquamous carcinoma
Basal cell adenocarcinoma
Carcinoma ex pleomorphic adenoma Intracapsular Invasive Metastasizing pleomorphic adenoma
Carcinosarcoma
Cribriform adenocarcinoma of minor salivary gland origin
Cystadenocarcinoma
Epithelial–myoepithelial carcinoma
(Hyalinizing) clear cell carcinoma
Intraductal carcinoma (low-grade cribriform cystadenocarcinoma; low-grade salivary duct carcinoma)
Lymphoepithelial carcinoma
Mammary analogue secretory carcinoma
Mucinous carcinoma
Mucoepidermoid carcinoma
Myoepithelial carcinoma
Neuroendocrine carcinoma
Small cell Large cell
Oncocytic carcinoma
Polymorphous low-grade adenocarcinoma
Salivary duct carcinoma
Sebaceous carcinoma/lymphadenocarcinoma
Sialoblastoma
Squamous cell carcinoma

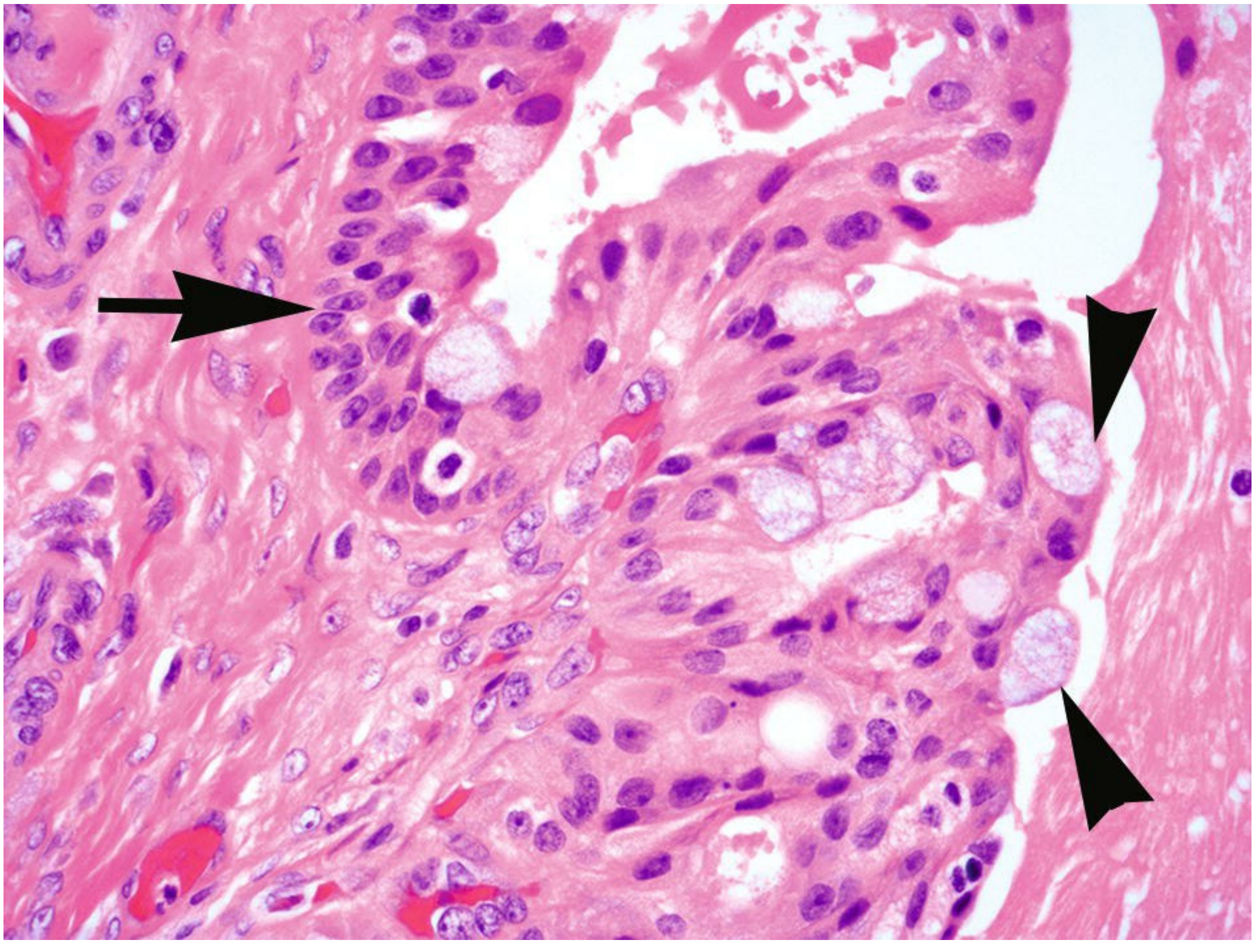


Figure 3.7 Mucoepidermoid carcinoma of the parotid gland demonstrating the classic admixture of cell types including mucocytes (*arrowheads*), epidermoid cells (*arrow*), and intermediate cells, the latter composed of cells that are more spindle shaped with hyperchromatic nuclei.

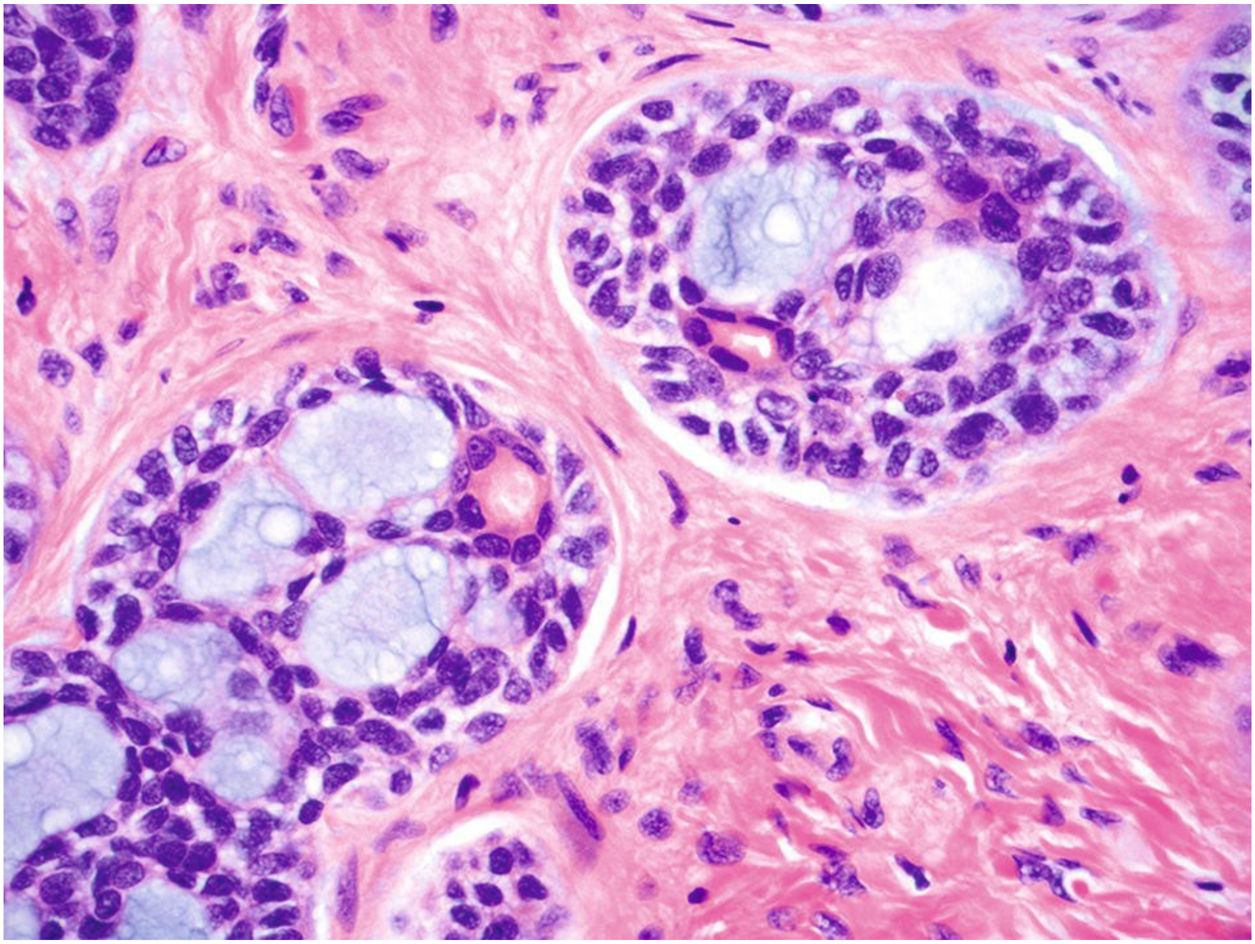


Figure 3.8 Adenoid cystic carcinoma with classic histology including the cribriform growth pattern ("Swiss cheese") predominantly composed of abluminal (myoepithelial) cells surrounding cystic spaces and less conspicuous but identifiable true glands surrounded by luminal (epithelial) cells.

The in-depth description of the many types of salivary gland carcinoma is beyond the scope of this chapter. However, recent studies have elucidated characteristic genomic alterations associated with several variants, which may enable improved diagnosis in future (Table 3.6).[144]–[159] Moreover, our improved ability to accurately segregate tumors by molecular alterations will enable more accurate prognostication.

Table 3.6 Chromosomal Rearrangements in Salivary Gland Neoplasia

	Chromosomal Rearrangement	Gene Fusion	Prevalence
Adenoid cystic carcinoma	t(6;9)(q22-23;p23-24)	*NFIB-MYB*	30%–50%
Hyalinizing clear cell carcinoma	t(12;22)(q13;q12)	*EWSR1-ATF1*	~90%
Mammary analogue secretory carcinoma	t(12;15(p13;q25)	*ETV6-NTRK3*	>90%
Mucoepidermoid carcinoma	t(11;19)(q21;p13)	*CRTC1-MAML2*	>60%
Pleomorphic adenoma	Rearrangement of 8q12[a] Rearrangement of 12q13-15[a]	*PLAG1*[a] *HMGA2*[a]	70%

[a]Multiple identified fusion partners.

Thyroid and Parathyroid Carcinomas.

Thyroid carcinoma is the most common endocrine malignancy. Tumors arise from either the follicular epithelium (papillary, follicular, poorly differentiated, and anaplastic thyroid carcinomas) or parafollicular C-cells of neuroectodermal origin (medullary thyroid carcinoma [MTC]) and have been shown to demonstrate specific genetic mutations (Table 3.7).

Table 3.7 Common Genetic Alterations in Thyroid Neoplasia

Tumor Type	Affected Genes	Prevalence
Follicular adenoma	*RAS*	10%
Noninvasive follicular thyroid	*RAS*	30%
Neoplasm with papillary- like nuclear features (NIFTP)	*BRAF* *PAX8/PPARγ*	<5% 20%
Follicular carcinoma	*RAS* *BRAF* *PAX8/PPARγ* translocation	45% <10% 35%–45%
Papillary carcinoma	*TRK*	<5%
Follicular variant	*RAS* *BRAF* *PAX8/PPARγ* translocation *RET/PTC* translocation	40% 10% 10% 3%
Classical variant	*RAS* *BRAF* *RET/PTC* translocation	1% 70% 10%
Poorly differentiated carcinoma	*RAS* *BRAF*	20% 20%
Anaplastic carcinoma	*RAS* *BRAF*	45% 25%
Medullary carcinoma		
Sporadic	*RET*	50%
Familial	*RET,* germ-line mutation	>95%

PTC is by far the most common variant of thyroid carcinoma, accounting for ~86% of thyroid carcinomas, with a rising incidence over the past few decades.[160,161] Controversy exists as to the cause of this dramatic increase.[160] Whereas some authors cite the improved ability to detect disease, and more frequent discovery of incidental thyroid nodules on imaging studies undertaken for other reasons.[161,162] It is now thought that the reported increase in carcinoma is due to overdiagnosis of indolent disease.[163,164] In particular, the non-invasive, encapsulated follicular variant of papillary thyroid carcinoma has been determined to have low risk of aggressive behavior and has been recently renamed as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[165] In addition, it is suspected that many incidentally discovered "microcarcinomas" found on resection for benign solitary nodule or multinodular goiter represent at best, premalignant change and, based on their benign behavior in recent series, should not truly be considered to be a true malignant disease.[166,167]

Classical papillary carcinomas are diagnosed based on their nuclear features on FFPE sections. These features include enlarged, pale to optically clear nuclei with peripherally located, small nucleoli and the presence of nuclear membrane irregularities typically visualized as longitudinal grooves and pseudoinclusions (Fig. 3.9). Clearing of the nuclei is an artifact of formalin fixation and is not seen in frozen sections, cytology preparations, or tumors fixed in other media.[101,168] Tumor cells often have abundant cytoplasm. The architecture of papillary tumors may be papillary or follicular; colloid is often scant. Intratumoral fibrosis and calcification is common. At the molecular level, classical PTC is characterized by a high frequency of mutations in the mitogen-activated protein kinase (MAPK) pathway, with activating *BRAF* mutations (most commonly n.T1796A (p.V600E)) accounting for nearly 70% of cases,[169–172] whereas *RET/PTC* gene rearrangements each account for 10% to 20% and *TRK* rearrangements for ~5%.[173] *RAS* mutations are rare in classical papillary carcinoma (Table 3.7).[172,174–179] Papillary carcinomas invade lymphatics early and spread to lymph nodes of the neck. Despite early nodal metastasis, papillary carcinomas have a relatively good prognosis. Survival is predicted by age and tumor size; younger patients have excellent long-term survival rates, whereas older patients and those with large primaries progress more rapidly.[180,181]

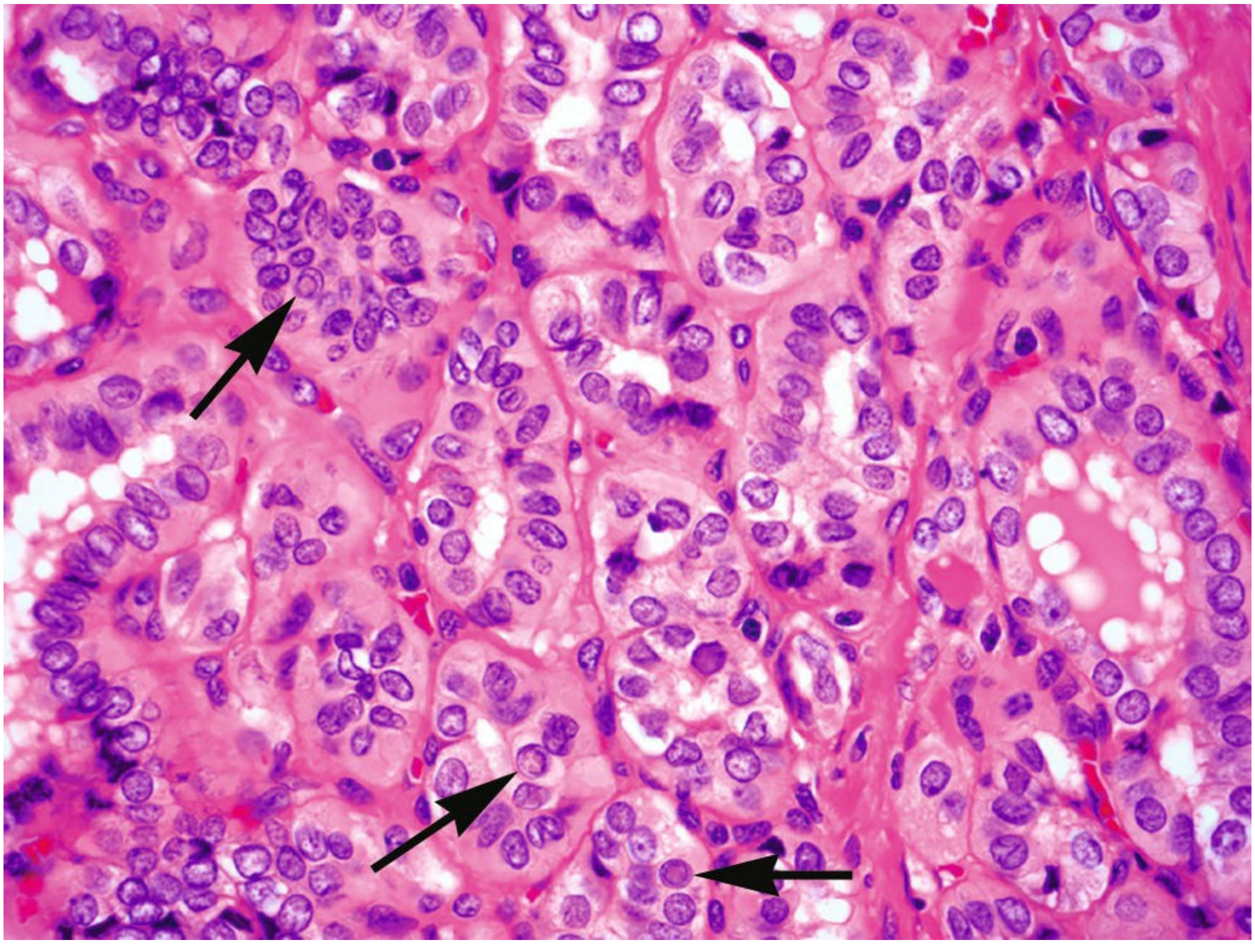


Figure 3.9 Papillary thyroid carcinoma. The diagnosis is predicated on the nuclear alterations including enlarged nuclei with variation in size and shape, very fine-appearing nuclear chromatin, overlapping, and crowding of nuclei, nuclear grooves, and nuclear (pseudo)inclusions (*arrows*).

Several variants of papillary thyroid carcinoma exist, the most controversial of which is the follicular variant papillary thyroid carcinoma (FVPTC). FVPTCs are distinguished by a lack of papillary architecture and subtle nuclear features of papillary carcinoma. The main differential diagnosis for invasive FVPTC is follicular carcinoma. Up until recently, encapsulated FVPTC without evidence of vascular or capsular invasion were also considered to be malignant despite low intraobserver agreement on the diagnosis.[182,183] However, increased recognition of the non-aggressive behavior of these tumors, and histologic and molecular similarity to follicular adenoma and carcinoma[175,184–186] has led to a new nomenclature of NIFTP. The new terminology was selected to reduce overdiagnosis of carcinoma and

overtreatment of a tumor which poses little risk to the patient.[166,187]

Follicular thyroid carcinomas constitute about 10% of thyroid malignancies.[160] Tumors typically have a microfollicular growth pattern and bland nuclear features, and are distinguishable from adenomas only by the presence of invasion. All solitary encapsulated nodules of the thyroid must have the entire capsule submitted for histologic evaluation, as the presence of either tumor invasion through the capsule into normal thyroid gland parenchyma or angioinvasion is diagnostic of malignancy (Fig. 3.10). Because they have a predilection for angioinvasion, follicular carcinomas spread hematogenously, generally bypassing regional lymph nodes to metastasize directly to the bone or lungs.[188] Subsequently, follicular carcinoma has a worse prognosis than does papillary carcinoma.[188] Follicular carcinomas have higher frequency of *RAS* mutations than do classical papillary carcinomas, with ~50% of tumors having activating mutation in *RAS* present. Another 35% or so are characterized by *PAX8/PPARγ* gene fusion.[189] Of note, *RAS* mutations are also seen in follicular adenomas and NIFTP and are not considered diagnostic for malignancy.[174]

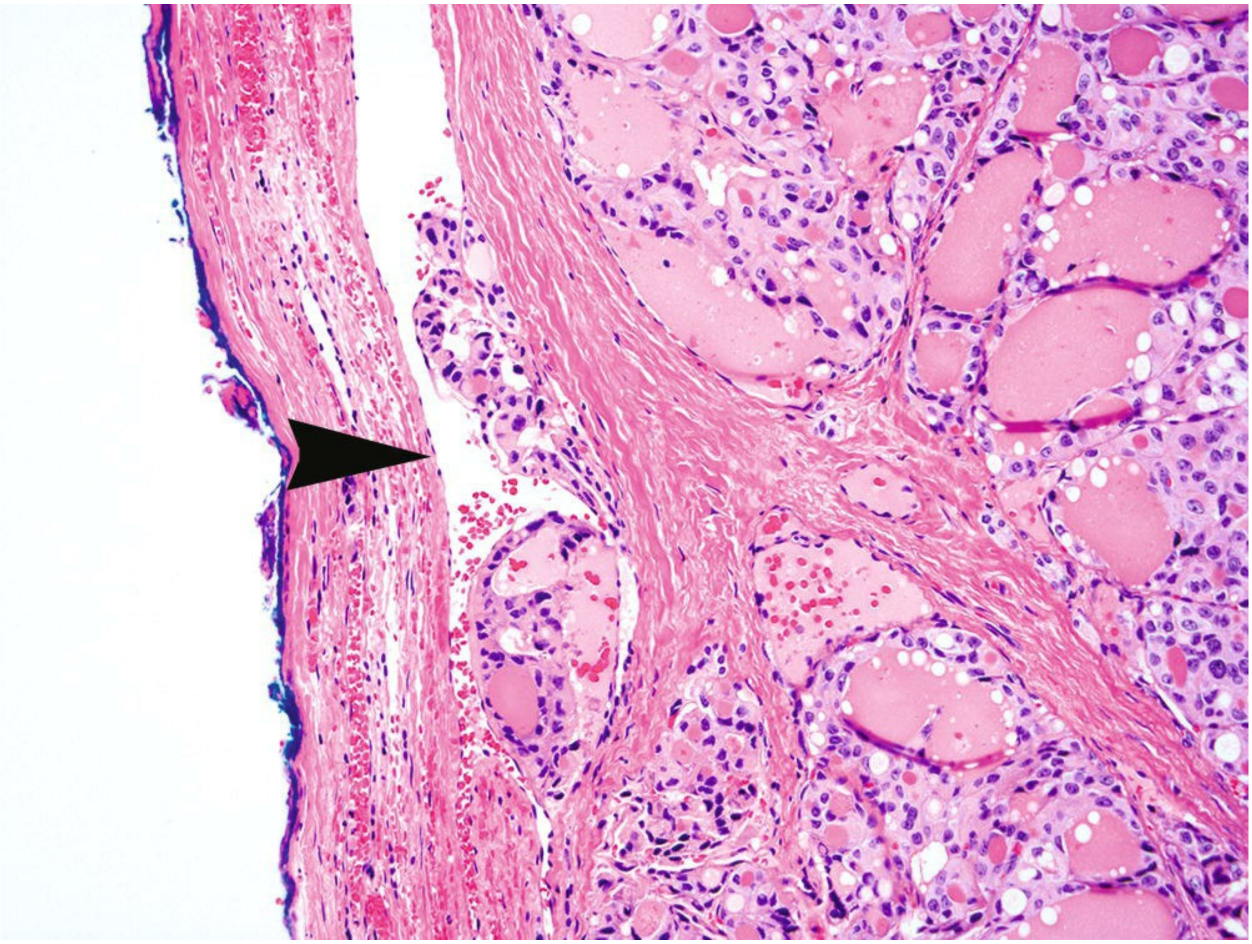
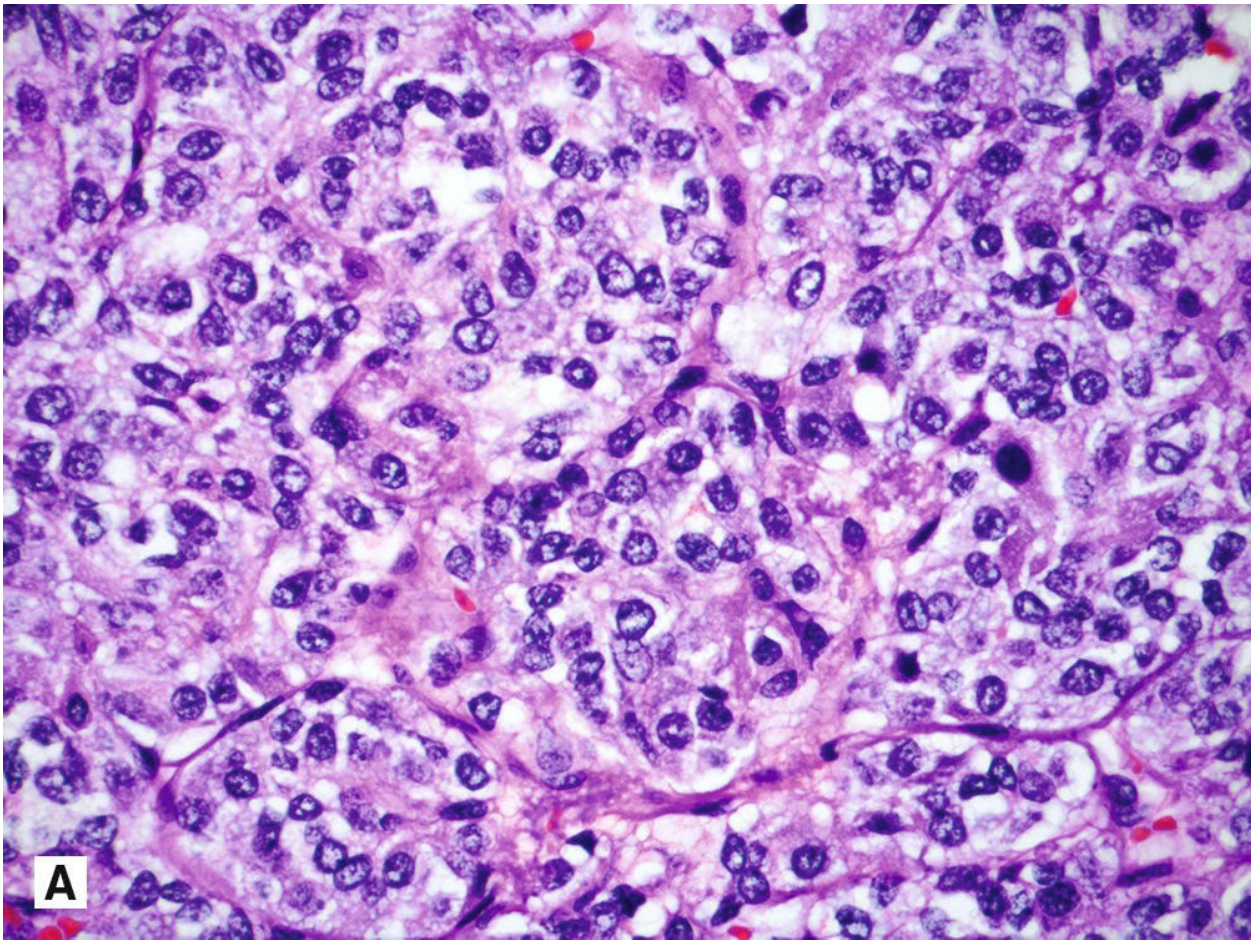


Figure 3.10 Follicular carcinoma. The tumor lacks nuclear features diagnostic for papillary carcinoma but shows an invasive growth pattern including invasion through the capsule and into an extracapsular endothelial-lined vascular space (*arrowhead*).

Anaplastic thyroid carcinoma is a rare, highly aggressive tumor, accounting for 1% of thyroid malignancies,[161] with a propensity to arise in elderly patients with long-standing thyroid disease. Anaplastic carcinoma presents as a rapidly growing mass in the neck, often with airway compromise, and by the time of presentation, is usually unresectable. One-year survival rates are as low as 35%,[190] and death is commonly due to local extension.[191] Histopathologic evidence of residual differentiated carcinoma suggests that anaplastic carcinomas arise in preexisting papillary or follicular carcinomas.[191] This theory is supported by molecular evidence of progressive genetic alterations as tumors advance from differentiated carcinoma to poorly differentiated carcinoma and anaplastic carcinoma.[176] Anaplastic carcinomas

display a variety of morphologies, from spindled, sarcomatoid cells, to large epithelioid cells, and some cases may show squamoid differentiation. One characteristic feature is a marked tumoral inflammatory response.

MTC constitutes about 2% of thyroid malignancies.[160] Whereas the majority of cases are sporadic, 20% to 40% are familial medullary thyroid carcinoma (FMTC).[192–194] Activating *RET* mutations are found in the majority of cases, with at least 39 different germ-line mutations described in familial cases (MEN 2A, MEN 2B, FMTC).[193,195,196] Familial tumors arise in younger patients (peaking in the fourth decade) and tend to be bilateral or associated with multifocal C-cell hyperplasia. Sporadic cases arise in the fifth to seventh decades and are usually solitary. Five-year survival rates approximate 85%.[196] Histologically, tumors have classical neuroendocrine appearance with abundant granular cytoplasm and round nuclei with “salt and pepper” stippled chromatin (Fig. 3.11A). Cells may be round, spindled, or plasmacytoid, whereas the stroma is frequently fibrotic and highly vascular. Calcitonin-derived amyloid deposition is a common feature (Fig. 3.11B).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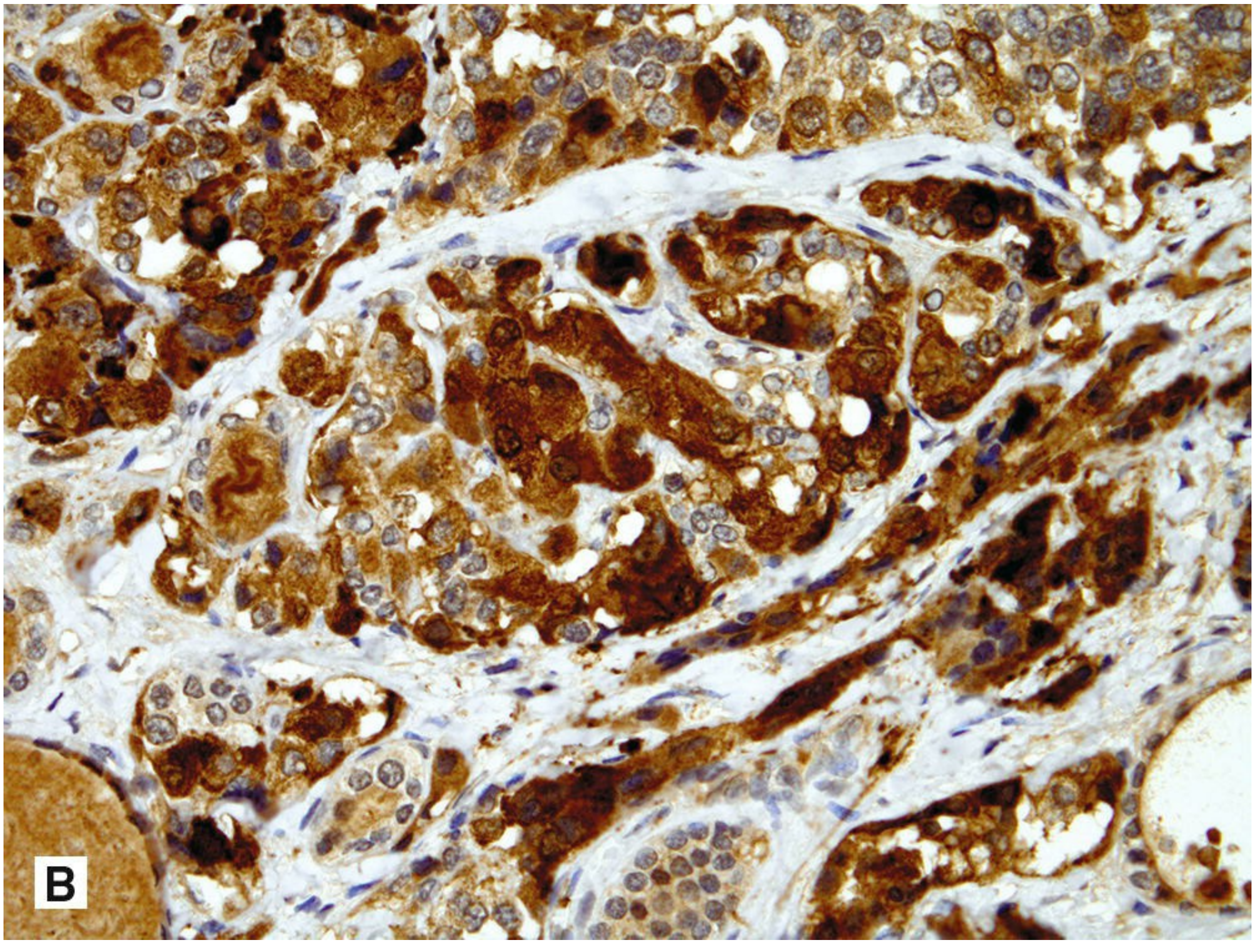


Figure 3.11 Medullary carcinoma of the thyroid. **A:** Intrathyroidal neoplasm characterized by organoid or cell nest growth pattern, absence of colloid formation, and presence of nuclei with stippled-appearing nuclear chromatin. **B:** Diffuse calcitonin immunoreactivity confirms the diagnosis; note the absence of calcitonin staining in residual thyroid follicular epithelial cells **(lower left)**.

Parathyroid carcinomas are very rare, accounting for <1% of parathyroid tumors.[197] Diagnosis requires close communication between the resecting surgeon and diagnosing pathologist. Parathyroid carcinomas produce very high elevations of parathyroid hormone to levels greater than typically seen in cases of hyperplasia or adenoma.[198] At the time of surgery, tumors are found to be densely fibrotic and may be difficult to resect from adjacent structures. This fibrotic reaction may be an indicator of invasion of thyroid or skeletal muscle, which, along with lymph–vascular invasion (LVI), are the only reliable histologically diagnostic features of parathyroid carcinoma (Fig.

3.12). In isolation, solid tumor growth, the presence of fibrosis, mitotic activity, and necrosis all suggest malignancy but are usually not adequate to make the diagnosis. Mutations in *CDC73 (HRPT2)*, the gene encoding parafibromin protein, are frequent in both sporadic and familial parathyroid carcinomas.[197] Presence of mutation is often reflected in the absence of parafibromin protein, a feature that may be detected by immunohistochemistry. Absence of parafibromin expression in borderline lesions possessing some, but not all of the features of carcinoma (atypical adenomas), may help support a diagnosis of malignancy.[199,200] The prognosis of parathyroid carcinomas depends on the success of resection, with lower recurrence rates (~30%) associated with preoperative diagnosis and complete en bloc resection.[197]

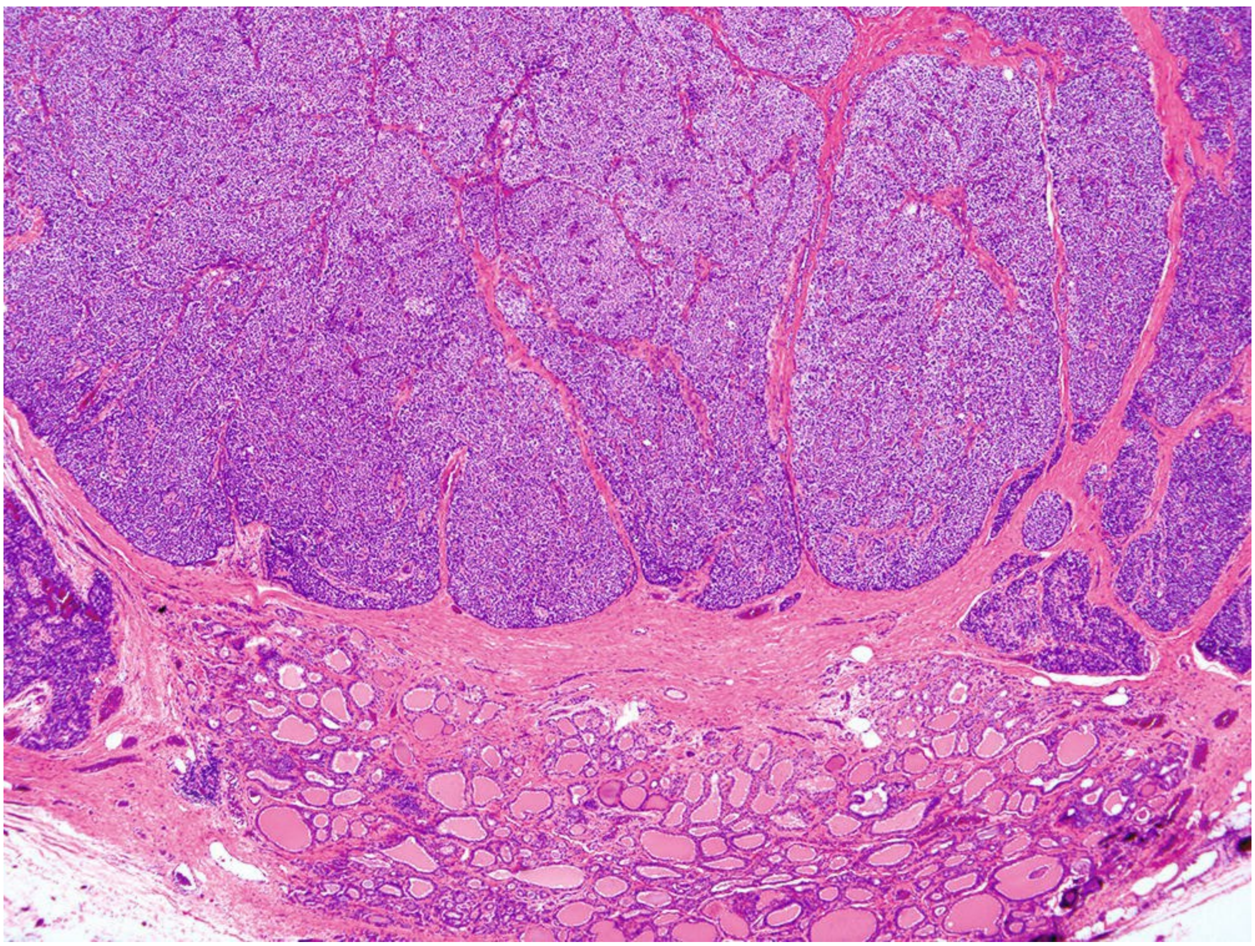


Figure 3.12 Parathyroid carcinoma. Clinically, the tumor was adherent to the thyroid gland necessitating ipsilateral lobectomy (inferior) and was histologically characterized by the presence of intralesional fibrosis creating a

nodular-appearing proliferation extending to the thyroid parenchyma.

Neuroectodemal and Neuroendocrine Malignancies.

Neural crest cells migrate throughout the body during development and are thought to be precursors to melanocytic cells, receptor and endocrine cells of perivascular glomus bodies, the olfactory sensory apparatus, and Merkel cells associated with cutaneous mechanoreceptors, among others.

Malignancies arising from sensory apparatuses, including paragangliomas and olfactory neuroblastoma, share similar histologic features with other neural crest–derived tumors such as MTC and pheochromocytoma. Tumors have a nested, highly vascular growth pattern, with balls of neoplastic cells surrounded by S100 protein–positive sustentacular cells. Malignant cells may display a wide spectrum of neuroendocrine differentiation, from bland cells with round nuclei and abundant granular cytoplasm, as in most paragangliomas, to aggressive-appearing small cells with scant cytoplasm, necrosis, and high proliferative index, as in high-grade olfactory neuroblastoma. Most tumors express neuroendocrine markers (e.g., chromogranin, synaptophysin), at least focally and typically lack immunoreactivity with epithelial-related markers (e.g., cytokeratins).

Neuroendocrine tumors of mucosal or salivary origin, while no longer thought to be of neural crest origin, demonstrate similar histologic and immunophenotypic features, although sustentacular cells are not present. Merkel cell carcinoma is a neural crest–derived small cell malignancy with a distinctive, perinuclear dot-like pattern of cytokeratin 20 expression,[201] as well as immunoreactivity with neuroendocrine markers (e.g., synaptophysin, others). Tumors arise in older individuals with a history of sun exposure and are commonly associated with immunocompromise, a finding explained by the discovery of the role of polyoma virus in Merkel cell carcinogenesis.[202] Immunoreactivity with the Merkel cell polyoma virus (MCPyV), a nuclear marker, is confirmatory of the diagnosis.

Mucosal melanoma is a rare, highly aggressive malignancy with poor survival rates. The head and neck is the most common site for mucosal melanoma, with tumors arising from melanocytes lining mucosal epithelium anywhere in the upper aerodigestive tract. Definite risk factors have not been

identified, and *BRAF* mutations are rare, although *KIT* mutations have been reported.[203] Thus, mucosal melanoma is considered a clinical entity distinct from cutaneous melanoma. Nevertheless, histologic and immunophenotypic features are similar, with many tumors displaying melanin pigment or antigenic evidence of melanogenesis.

Clinicopathologic correlation on small biopsy specimens is key in determining the correct workup for the diagnosis of small cell malignancy with neuroendocrine appearance. Age, site, and radiographic characteristics all play a role, and a diagnosis should never be made in isolation.

Mesenchymal Malignancies.

Mesenchymal tumors include those arising from connective tissues or bone or that recapitulate stages of mesenchymal differentiation. Lipomas are the most common benign mesenchymal tumor, followed by schwannoma/acoustic neuroma. Malignant mesenchymal tumors (sarcomas) are exceeding rare but are responsible for high morbidity and mortality when they occur, due to the complex anatomy of the region and difficulty in obtaining complete resection. Osteosarcomas typically arise in the jaw, whereas both chondrosarcoma and chordoma affect the skull base. Angiosarcoma is predisposed to arise in sun-damaged skin of the scalp, whereas rhabdomyosarcoma has a predilection for the sinuses. Although discovery of characteristic molecular alterations in many entities has improved diagnosis of mesenchymal tumors, undifferentiated or unclassifiable tumors with no known distinguishing morphologic, immunophenotypic, or molecular alterations remain a particular problem and often are unresponsive to adjuvant therapy.

Radiation-induced sarcomas are a rare secondary complication of radiation therapy for primary epithelial malignancies. Secondary sarcomas occur with variable latency period after radiation, from ~5 years to decades following therapy, and occur within the radiation field. Radiation-induced sarcomas tend to be aggressive and commonly take the form of osteosarcoma (if arising from bone), angiosarcoma (in the skin), or undifferentiated sarcoma, although other variants have been reported. Clinical correlation is required to establish the diagnosis.

Hematolymphoid Malignancy.

Lymphomas account for ~5% of all malignancies of the head and neck and are often subclassified as Hodgkin and non-Hodgkin lymphomas. The 2008 World Health Classification of Tumours recognizes over 50 subtypes of non-Hodgkin lymphoma,[204] nearly any one of which may present in the head and neck. The most frequent types of non-Hodgkin, B-cell, and T-cell lymphomas seen in this region are B-lymphoblastic leukemia/lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), extranodal mucosa-associated lymphoid tissue (MALT) B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, Burkitt lymphoma, and nasal extranodal NK/T cell lymphoma.[205] The head and neck is rich in lymphoid tissue, and lymphoma should be kept in mind in the differential diagnosis of cervical lymphadenopathy or asymmetrical tonsillar hypertrophy within Waldeyer ring in the adult population. Lymphomas may also arise secondary to long-standing chronic autoimmune inflammatory disease such as Hashimoto thyroiditis or Sjögren syndrome.[205] EBV infection can be associated with lymphomas of the head and neck, with the most aggressive form arising in extranodal NK/T cell lymphoma, nasal type (formerly referred to as lethal midline granuloma, among other terms).[206,207]

Correct diagnosis of lymphoma is highly dependent on adequate sampling and tissue preservation. When lymphoma is suspected, tissue must always be sent fresh, with the differential diagnosis clearly indicated on the requisition, to ensure that tissue is triaged for flow cytometry or molecular studies, as appropriate.

Differentiation (Grade)

Histologic grade is used to describe how well differentiated a malignant tumor is, that is, how well it recapitulates normal tissue. Although grade has been applied to all types of malignancies, it is not always applicable, particularly in mesenchymal tumors that may have intrinsic biologic potential independent of grade, for example, angiosarcoma, or that may not resemble any known normal tissue type. Epithelial malignancies are highly amenable to grading, as they are readily comparable to normal epithelium. A well-differentiated, "low-grade" keratinizing squamous cell carcinoma shows obvious keratinization and intracellular bridges and may grow in a more cohesive pattern, whereas poorly differentiated "high-grade" tumors progressively lose these features and tend to grow in a less cohesive,

infiltrative pattern.

At the extreme end of the spectrum, undifferentiated, anaplastic tumors lose all resemblance to the putative lineage of differentiation. Undifferentiated carcinomas mimic mesenchymal tumors, in that the malignant cells become discohesive, develop a spindled morphology, and commonly express mesenchymal markers such as vimentin, rather than cytokeratins specific of epithelial origin. Historically, the term “dedifferentiated” has been used for these tumors in the belief that the cell of origin had undergone progressive phenotypic losses. More recently, the term “epithelial to mesenchymal transition (EMT)” became popular to explain the phenomenon and account for cell motility.[208] Both terms are, to some extent, misnomers. Mounting evidence suggests that the cell of origin for carcinoma is a pluripotent stem cell.[209,210] In well-differentiated carcinomas, this neoplastic cell produces a clone capable of nearly complete epithelial differentiation but characterized by abnormalities in proliferation, survival, and migration.[209,211] Over time, progressive molecular alterations in mitotically active cells produce a clone, which is unable to fully differentiate but may have survival, migratory, or proliferative advantages over better differentiated subclones within the tumor.

Poorly differentiated tumors present diagnostic difficulties and often require ancillary studies such as immunohistochemistry, electron microscopy, or molecular analysis to elucidate evidence of a line of differentiation. These techniques are discussed in greater detail in “Ancillary Studies (Pathologic Toolbox) and Applications” section, below. An attempt to make a definitive diagnosis is key, as undifferentiated “spindle cell” squamous cell carcinoma has a distinct biologic behavior different than that of most spindle cell sarcomas and will respond differently to adjuvant therapy. In some cases, evidence of epithelial origin may be completely lost, resulting in false-negative diagnostic studies. In such cases, a high index of suspicion based on the clinical features and site of origin may still result in the correct diagnosis being made.

Poorly differentiated (high-grade) tumors are thought to behave more aggressively than do well-differentiated tumors.[212] Therefore, grading can assist with prognostication. Each different lineage of tumors has general grading criteria, and some individual tumor types have specific grading criteria. Grading criteria that rely on objective factors, such as the number of

mitotic figures, presence of necrosis, extent of nuclear atypia, or specific growth patterns as with mucoepidermoid carcinoma or adenoid cystic carcinoma,[213–217] tend to perform better in prognostication than do poorly reproducible subjective systems such as are used for squamous cell carcinoma.[218,219] Nevertheless, a considerable degree of subjectivity in assessment remains. Another important consideration is that high-risk prognostic features such as lymphatic or perineural invasion may supercede the relevance of grade in predicting tumor behavior, particularly in low-grade carcinomas. In oral squamous cell carcinoma, higher grade is generally associated with higher-stage disease[220] and may predict poor survival, although differing methodologies of grading make comparisons between studies difficult.[219,221,222]

Staging (TNM)

Staging systems are used to describe the anatomic extent of a malignancy. Staging criteria are based either on the specific subtype of malignancy or on tumor site. Although clinical and pathologic staging systems both report the same components, they may produce different results, due to the ability of histopathologic review to detect subtle, clinically occult involvement by tumor. Staging reflects three aspects of tumor spread: T—local extent of the primary tumor, N—presence and extent of involvement of regional lymph nodes by tumor, and M—presence or absence of distant metastases.[223] These parameters have largely been shown to predict outcomes in squamous cell carcinoma, and TNM staging is widely used for routine cancer management.

Tumor Site

The majority of TNM staging criteria are based on primary tumor site rather than on histologic subtype. Thus, cancer of the oral cavity is staged differently than cancer of the larynx, with criteria refined to better stratify for risk as emerging studies contribute to a better understanding of disease. Site groupings are important to take into account both the biology of tumors common at these sites as well as typical patterns of nodal or distant metastasis. Site is also critical in early diagnosis. Tumors that are visible to patients (cutaneous malignancies) or that present with symptoms in early stage of disease (e.g., tumors arising on the true vocal fold) are much more likely to be detected at an early stage when curative therapy is possible.

Tumors arising in occult locations such as sinus, tonsils, or hypopharynx, on the other hand, may not come to clinical attention until an advanced stage tumor causes obstruction or palpable nodal metastases. Site is also important as the etiology and natural behavior of squamous cell carcinoma arising in the oropharynx is distinct from those arising in the oral cavity, nasopharynx, or glottis. Site, therefore, has been reported as an independent prognostic factor in and of itself[224,225] and must be taken into account when assessing patient outcomes.

Tumor Size

Extent of primary disease is based on tumor size and involvement of adjacent structures. In most sites of the head and neck, a low-stage (pT1) tumor is one that is no more than 2 cm in maximal dimension, whereas a high-stage (pT3) tumor is large (>4 cm). Small tumors may be upstaged if they show evidence of aggressive behavior, such as invasion through cortical bone in oral carcinomas (pT4a), or extension to perithyroidal soft tissues in carcinoma of the thyroid (pT3).[223] Tumor size generally correlates with resectability; larger tumors are more likely to have positive margins at resection[80,226] and are thus at higher risk for local recurrence and death.[120,227] Size is not the only predictor of aggressive behavior; as further discussed below, additional criteria factor into determining biologic behavior, and some small tumors behave in a highly malignant fashion whereas other large, but superficial tumors may be quite indolent.

Lymph Nodes

Presence of tumor metastasis in cervical lymph nodes has been shown to be the single most important adverse prognostic factor in squamous cell carcinoma of the head and neck.[228–230] In patients with lymph node metastases, 5-year overall survival drops to 59%, compared to 82% for patients with node-negative disease.[231]

Whereas clinical staging relies on radiographic (CT, MRI, ultrasound, and positron emission tomography [PET]) evidence of nodal involvement (enlarged, metabolically active nodes) or the presence of a palpable mass in the neck, pathologic node staging has the ability to detect subcentimeter micrometastases and isolated tumor cells within lymph nodes. Number, size,

and laterality of nodal involvement all contribute to stage,[223] with larger metastases and contralateral or bilateral metastasis portending worse outcomes.[232]

Conventional nodal staging may not be appropriate for oropharyngeal HPV-associated carcinomas, as metastases are frequently bilateral due to the location in the midline base of tongue, and may be large due to cystic change. As such, the present AJCC 7th edition staging system[223] has been shown to have poor correlation with survival in HPV-associated carcinoma.[233] Some investigators have proposed a new staging system for HPV-associated carcinoma to reflect the better prognosis for patients presenting with nodal metastasis compared to conventional squamous cell carcinoma.[234] However, such proposals may be premature until it is determined if therapy for HPV-associated carcinomas can be safely de-escalated relative to conventional squamous cell carcinoma.

Recent studies to further refine nodal staging criteria have investigated the prognostic value of number of positive lymph nodes in head and neck cancer. Because the number of positive nodes may increase with the completeness of node dissection and identification, the lymph node ratio (total positive number of nodes divided by total nodes found) is used to normalize reporting. High lymph node ratio has now been reported to be independently predictive of poor outcomes in patients with oral cancer and nodal metastasis and may perform better in risk stratification than does N classification.[235–239] Lymph node ratio is also prognostic in cancer of the larynx,[240] postchemoradiotherapy squamous cell carcinoma of the hypopharynx,[241] and carcinoma of the oropharynx.[242]

Although not considered a factor in lymph node staging, cervical level of nodal involvement is also important. Long-standing and aggressive tumors will progressively spread from upper levels to lower levels along normal lymphatic drainage channels, leading to higher disease burden, and worse outcomes.[232,243–245] Quantitatively, patients with multiple levels involved have been reported to have twice the risk of distant metastasis compared to patients with only one level (36% vs. 18%).[225] In addition, level of involvement may be important for determining radiation fields and dosage when planning adjuvant therapy.[246]

Ideally, each anatomic lymph node level is identified by the surgeon at

the time of dissection and sent separately for pathologic evaluation,[247] as selective dissections do not provide anatomic structures required for accurate orientation and level assessment. Intact radical neck dissections do not require orientation for pathologic determination of levels during specimen processing. Lymph node size and number is documented grossly by the prosecting pathologist. If grossly identified, the size of the largest metastatic focus should be measured and gross extracapsular extension or the presence of lymph node matting documented. Although matting may convey a worse prognosis, for documentation purposes, matted lymph nodes are counted as a single metastatic focus. All identified lymph nodes are submitted for histologic evaluation. If few nodes are identified, the remaining adipose tissue from the neck is submitted to search for microscopic lymph nodes. Thorough neck dissection of all five cervical levels should yield 30 to 50 lymph nodes, on average.[247]

Tumor deposits in soft tissue may represent completely replaced lymph nodes,[248] or possibly vascular invasion, and present a similar risk for relapse as a lymph node with extracapsular spread (ECS).[249]

Sentinel Lymph Node Biopsy.

Sentinel lymph node biopsy is commonly used to accurately evaluate the necessity of regional lymph node dissection in malignancies such as melanoma and breast carcinoma.[250,251] In the head and neck, the role of sentinel node biopsy as an alternative to neck dissection in clinically N0 squamous cell carcinomas continues to be an evolving field.

Sentinel node biopsy relies on the concept that lymphatic drainage follows an orderly progression, with tumor first spreading to the most proximal catchment basin before subsequently involving more distal levels.[252] The lymph nodes in this proximal field are designated the sentinel lymph nodes and may be identified by injecting the area around the tumor with radioactive ^{99m}Tc–labeled colloid tracers and/or dye prior to surgery and selectively harvesting all nodes subsequently found to contain tracer after a specified time has elapsed.[253] Ideally, these nodes are the most likely to reflect the true disease status, and if all such identified sentinel nodes are negative for carcinoma, then further neck dissection is unnecessary, as the tumor will not have spread further.[254,255] Sentinel node biopsy, therefore, improves staging over radiographic/clinical N stage, while preventing

unnecessary surgical morbidity due to extensive neck dissection—morbidity that has been shown to significantly affect quality of life.[255–259]

Most institutions routinely perform elective neck dissection for clinical T1/T2 N0 oral and oropharyngeal carcinomas. This procedure allows for nodal staging and clears radiographically occult disease. However, only 25% to 30% of patients are reported to have occult neck disease after complete pathologic evaluation,[260–262] resulting in "unnecessary" neck dissection in the remaining 70% to 75%. Several prospective multi-institutional trials have confirmed the predicted distribution patterns of nodal metastasis in oral cancer and reported sentinel node biopsy to have a negative predictive value (NPV) of ~96% for nodal metastasis.[263,264] Civantos and coauthors reported a 26.4% rate of positive sentinel nodes, whereas Alkureishi et al. found positive sentinel lymph nodes in 34% of patients, on par with the expected rate of occult disease in clinical N0 patients. These two studies confirmed the results of a number of smaller single-institution series, which found the NPV of sentinel node biopsy to be between 90% and 98%, with false-negative rates of <6%.[265–273]

Methodologies used for evaluation of sentinel node vary and may have an impact on the sensitivity of biopsy. Examination of one H&E level only, as was initially performed at submitting institutions in one recent study, resulted in an NPV of 94% for nodal metastasis.[263] With subsequent sectioning at 2 to 3 mm, and evaluation using immunohistochemical studies for four different cytokeratins, five cases were reclassified. Two cases positive for micrometastases at referring centers were negative in tissue available for central review, and in three initially negative cases, micrometastases were identified on immunohistochemical stains.[263] Several protocols advocate the evaluation of sentinel nodes using initial 2- to 3-mm gross sectioning followed by 150-μm step sections with serial sections cut at each level for H&E and immunohistochemical evaluation.[274,275] This protocol results in increased sensitivity for micrometastases.[264,276] However, because such extensive procedures are not used in routine lymph node dissections to detect micrometastases or isolated tumor cells, the true prognostic significance of their detection in sentinel nodes remains unclear.

Sentinel node biopsy may be less sensitive for occult nodal metastases in tumors arising in the floor of mouth, although data are limited.[263,264] False-

negative results in sentinel node biopsy may be due to procedural factors relating to injection and detection of radionuclide/dye tracer, lymphatic obstruction by tumor, particularly with bulky disease,[274,277] or analytical factors relating to node sectioning and size of metastasis. Sentinel node biopsy is not recommended for T3/T4 primary tumors.[274]

The use of frozen section has been evaluated for sentinel node biopsy, with reported NPVs of ~92% to 94% after taking into account patients with negative sentinel nodes who later developed neck recurrence.[112,278,279] Sentinel node biopsy has not been extensively validated for carcinomas of other sites, for example, larynx, or for HPV-associated carcinomas of the oropharynx.

Extracapsular (Extranodal) Spread.

ECS of lymph node metastasis occurs in between 41% and 85% of conventional squamous cell carcinoma of the oral cavity and larynx.[280–282] The presence of ECS in any node is associated with increased frequency of distant metastasis and more rapid locoregional recurrence and portends poor survival in conventional squamous cell carcinomas of the larynx[280,283,284] and oral cavity.[228,281,285–289] Because ECS predicts locoregional recurrence, it is considered to be an indication for aggressive postoperative radiation or chemoradiation therapy.[228,287,290,291]

Macroscopic ECS is detectable clinically as enlarged, fixed nodes or as lymph node matting. As ECS is seen in up to 75% of lymph nodes larger than 3 cm,[284,286,292,293] it is unclear if this finding has independent prognostic significance in the context of a stage pN3 neck. Microscopic ECS is present in 17% to 48% of subcentimeter nodes (Fig. 3.13),[284,286,294] and, in this context, it is associated with increased regional relapse.[295] Controversy exists as to the significance of extent of extranodal spread, either loosely defined as "macroscopic" versus "microscopic"[296,297] or measured more precisely as the perpendicular distance in mm from lymph node capsule, with or without desmoplastic stromal reaction.[288,295]

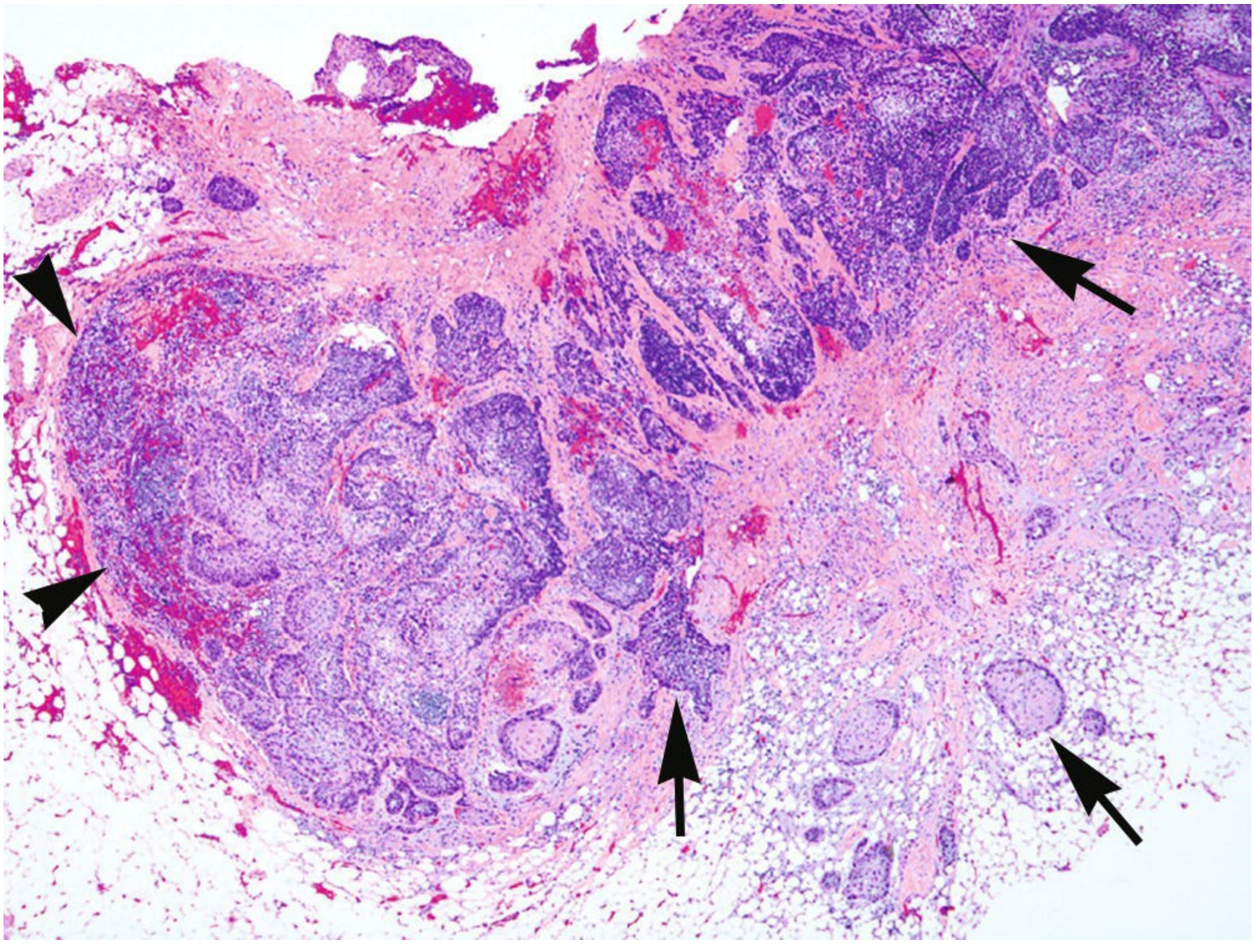


Figure 3.13 Extracapsular speed (ECS). At low magnification, residual lymph node parenchyma (*arrowheads*) is present with near complete effacement by metastatic squamous cell carcinoma, the latter extending into perinodal soft tissues (*arrows*).

The prognostic impact of ECS in HPV-associated oropharygeal squamous cell carcinoma is less certain than that for conventional keratinizing squamous cell carcinoma. One study, using a novel grading system for ECS, reported that only complete lymph node eradication (“soft tissue metastasis”) had prognostic value in univariate analysis of p16-positive oropharyngeal carcinomas, but this lacked independence in multivariate analysis.[298] In a follow-up study by the same group, 82% of 152 p16-positive oropharyngeal carcinomas were reported to have ECS (of which the researchers considered only 52% to represent “true” ECS). No prognostic significance was found for ECS, and moreover, in contrast to keratinizing squamous cell carcinoma, aggressive adjuvant therapy conveyed no additional benefit.[299] More

recently, a study comparing p16-positive carcinomas of the oropharynx with p16-negative carcinomas of the same subsite found no prognostic significance of ECS on disease-specific survival in either type.[300]

Cystic Lymph Node Metastasis.

Cystic metastases from squamous cell carcinoma were historically thought to represent carcinoma arising in a branchial cleft cyst—so-called branchiogenic carcinomas.[301] Subsequent investigations revealed an oropharyngeal primary tumor in nearly all cases.[23,302,303] Approximately 40% to 60% of lingual or palatine tonsillar squamous cell carcinomas present with at least one cystic metastatic lymph node and up to 36% with cystic metastases only.[304,305] Both primary and metastatic tumors are usually p16 and HPV positive.[305] Although PTC may also develop cystic metastases, other mucosal primary sites of the head and neck are only rarely, if ever, associated with cystic metastases.[305] Cystic metastasis should be clearly distinguished from centrally necrotic solid metastases, which are not necessarily associated with HPV infection.[305]

Distant Metastases.

Squamous cell carcinoma of the head and neck only rarely presents with distant metastases, with reported incidence rates ranging from 2% to 24%.[306–308] Rate of distant metastases is associated with extent of locoregional spread, and increased risk is seen in locally advanced disease (T3/T4), patients who present with lymph node metastases, hypopharyngeal primary site, and locoregional recurrence.[306] Multiple metastatic nodes, ECS, and inferior level neck nodal metastases have variously been found to be significant predictors of distant metastasis.[228,285,306,309] Distant metastases convey a poor prognosis, with 5-year survival rates of only 36% for oral, pharyngeal, or laryngeal squamous cell carcinoma metastatic at presentation.[231] Even in contemporary series, median survival rates for patients with distant metastases are only 8 to 9 months.[308,310] Patients with HPV-associated carcinomas have a slightly better prognosis with median survival rates of up to 19 months after development of distant metastases.[310]

The most common sites of distant metastases for head and neck squamous cell carcinoma are lung (50% to 70% of cases), bone (20% to

30%), and liver (5% to 10%).[307] Care should be taken to exclude a second primary tumor in the case of lung metastases, and morphologic and molecular correlation between the two tumors may be helpful, particularly in the case of HPV-related oropharyngeal tumors. In some cases, it is not possible to distinguish primary lung squamous carcinoma from a metastasis.

Additional Parameters

Tumor Thickness

Tumor thickness is a prognostic variable in T1 and T2 oral squamous cell carcinomas. Thickness is measured perpendicularly from the tumor surface (preferably using an ocular micrometer) to the deepest point of invasion and recorded in millimeter.[311–313] This is distinct from the depth of invasion that measures tumor depth relative to normal epithelium and may be recorded from the basement membrane of adjacent, noninvasive epithelium, or defined in terms of presence or absence of skeletal muscle invasion.[120,314] In the oral cavity, tumor thickness of 4 to 5 mm or more is associated with up to 60% risk of nodal metastases,[311,315–317] whereas microinvasive tumors with thickness of no more than 1.5 to 2 mm develop nodal metastases in <2% of cases.[311,312] Prognostic value of tumor thickness is independent of stage and, at least in T1/T2 oral squamous cell carcinoma, is more predictive of outcome than T stage.[311,312,318] Other studies of tongue, floor of mouth, palate, and lip have, in general, reported similar results, although methodologies for measuring tumor thickness varied between studies, as did cutoffs for significant thickness in predicting occult metastases.[313,315–330]

Of note, although the concept of tumor thickness as a prognostic factor was first used for cutaneous melanomas[331,332] and subsequently tested in carcinomas, it does not apply to risk assessment of mucosal melanomas.[333]

Patterns of Invasion

All invasion is not the same. Slow-growing, cohesive tumors, such as verrucous carcinoma, advance into underlying soft tissue with a broad, pushing tumor front while maintaining relatively normal patterns of squamous maturation toward the mucosal surface. Well-differentiated squamous cell carcinomas may invade as variably-sized, rounded nests,

which maintain relative maturation and polarity and remain closely apposed to the main bulk of tumor. These patterns are thought to represent less aggressive patterns of disease. Small nests, single cell infiltration of stromal tissues, and dispersed patterns of invasion with widely separated satellite foci characterize more aggressive disease (Fig. 3.14). Tumors with the most aggressive growth pattern (dispersed growth) are associated with increased local recurrence[334] and worse overall survival.[335]

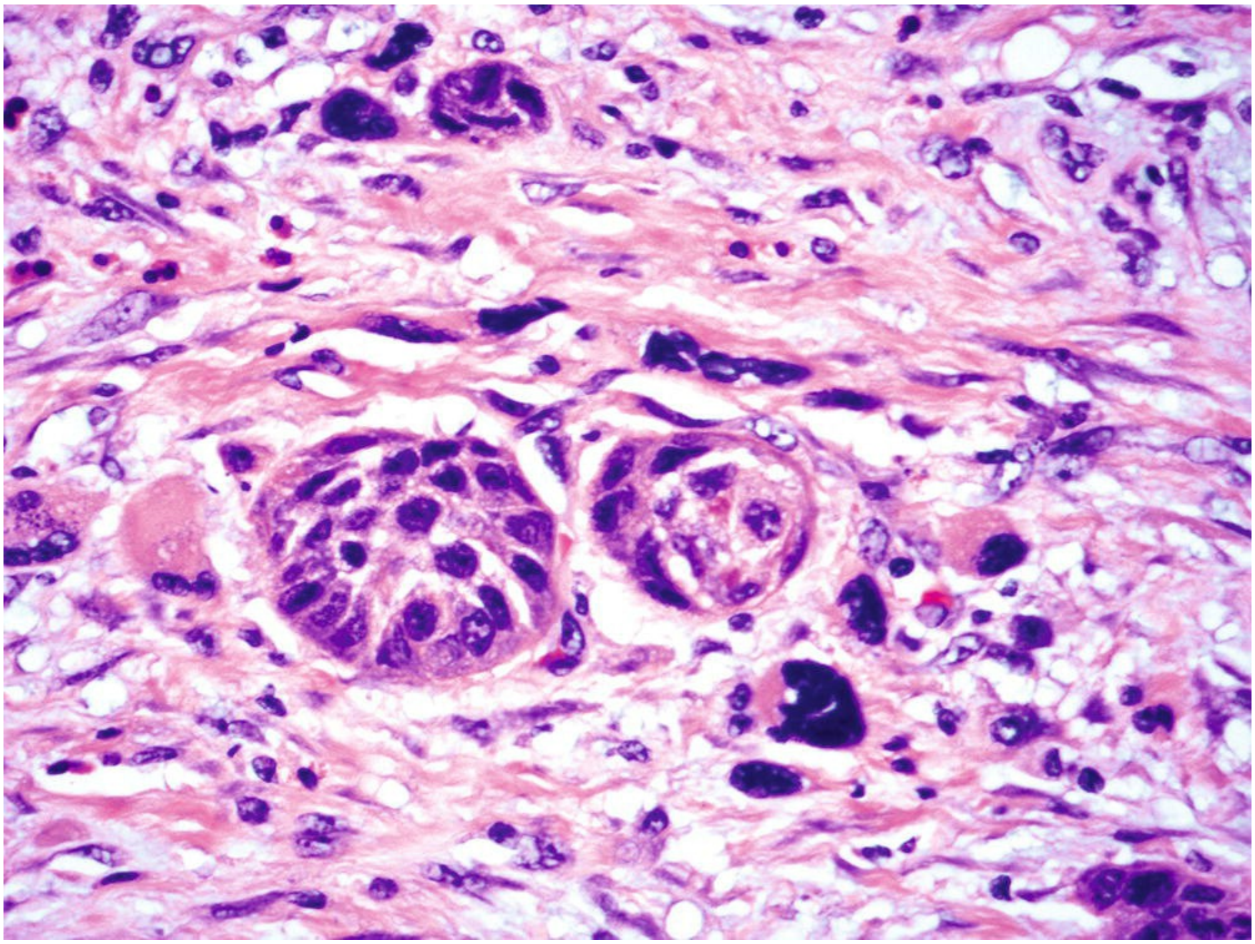


Figure 3.14 Infiltrative squamous cell carcinoma in which the carcinoma invades as cohesive cell nests as well as individual (dyscohesive) malignant cells.

Inflammatory Response

Inflammatory response to tumor is thought to be a sign of active immune defense against malignant cells. Early studies of floor of the mouth T1–T2 tumors demonstrated that tumors with the least amount of inflammatory

response were most likely to develop nodal metastases.[311,336] Subsequent studies have further refined understanding of this phenomenon. Currently, activated cytotoxic tumor-infiltrating T lymphocytes (TILs) are thought to be the important drivers of autoimmune response to malignancy. Studies have shown that increased density of CD3+ and CD8+ TILs predicts improved overall survival in patients treated with curative intent.[337,338] HPV-associated oropharyngeal carcinomas are also reportedly associated with increased T cells, particularly CD3+, FoxP3+, PD-1+, or CD8+ T-cells,[339–341] a finding that has been suggested to contribute to their favorable prognosis.[342] It is hypothesized that response to viral antigens is the stimulus for this aggressive antitumor immune response.[343]

Other studies have found that the presence of increased peritumoral neutrophils[344] or high neutrophil-to-lymphocyte ratio within peripheral blood are poor prognostic features for head and neck squamous cell carcinoma.[345,346] Eosinophilic infiltrates, although commonly seen in invasive oral squamous cell carcinomas,[347,348] have not been clearly shown to have prognostic implications.[349–352]

Aggressive tumors are thought to exert potent immunosuppressive effects on the tumor microenvironment.[353] It is hoped that reversal of this immunosupression will result in more effective antitumor response during the course of tumor therapy.

Lymph–Vascular Invasion

Invasion of lymph–vascular spaces is a widely cited risk factor for poor outcomes (Fig. 3.15).[334,354–356] However, large contemporary series have reported conflicting findings. In one recent analysis of buccal carcinoma, no patients with LVI survived to 5 years, whereas 64% of those without did.[120] Nevertheless, in multivariate analysis, LVI was not an independent prognosticator; only T classification, margin status, and treatment modality predicted overall survival.[120] Vincent and coauthors reported similar findings in late-stage (T3/T4) oral carcinomas,[227] and Lee et al.[308] found that LVI did not independently predict distant metastasis in a large Korean series.

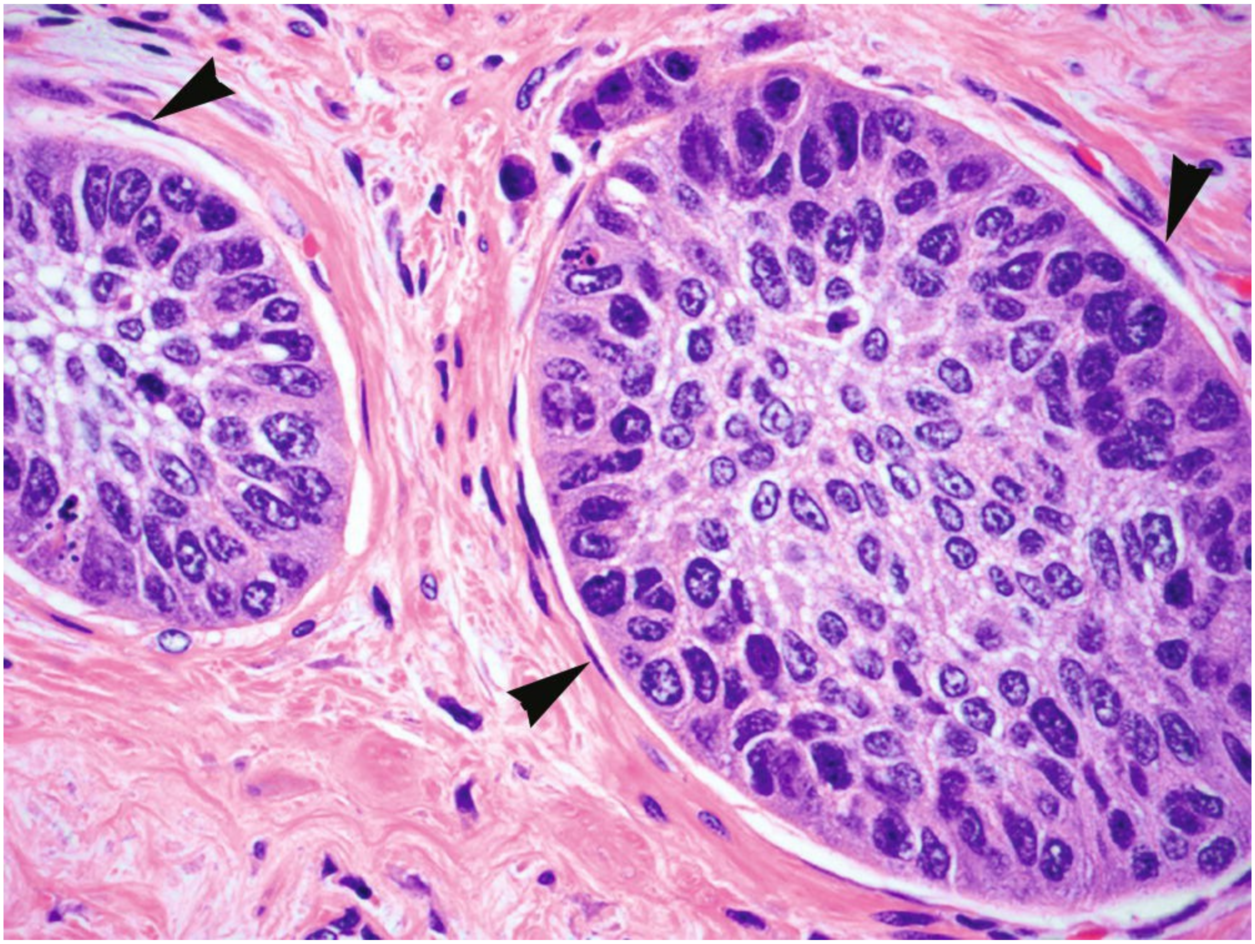


Figure 3.15 Lymph–vascular invasion. Foci of squamous cell carcinoma completely filling and adherent to the wall of the involved lymph–vascular spaces; the latter shows the presence of residual endothelial cells (*arrowheads*) allowing for their identification even in the absence of immunohistochemical staining for endothelial-related markers (e.g., CD31, others).

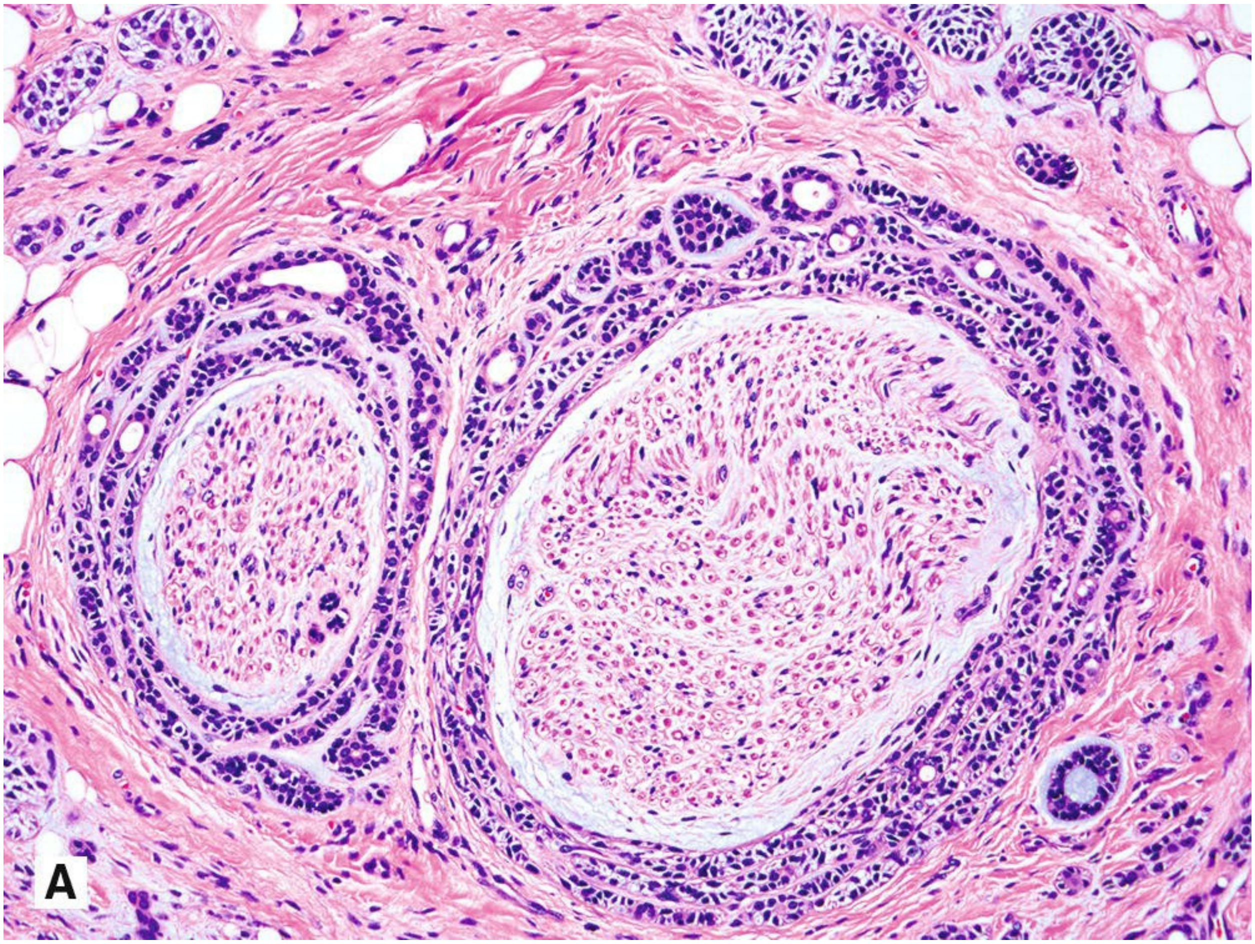
Some investigators have made the distinction between lymphatic and vascular invasion, again, with contradictory results. In some series, lymphatic involvement was not an independent prognosticator, but microvascular invasion predicted locoregional recurrence and death.[357,358] In contrast, Liao et al.[359] found that both lymphatic invasion and microvascular invasion were adverse prognostic features in stage III/IV oral tumors. Brandwein-Gensler et al.[335] reported that the presence of LVI was a negative sign, independent of both tumor grade and nodal metastasis, whereas Michikawa et al.[358] (2012) found lymphatic invasion to be a risk factor for nodal metastasis.

One possible explanation of the contradictory findings is that they are due to difficulties in distinguishing lymphatic from microvascular invasion on H&E-stained slides, as well as varying methodologies, tumor stages, disease sites, outcome end points, and population sizes used in different series to achieve their conclusions. Some authors relied on immunohistochemical studies to distinguish lymphatics from vascular channels, whereas in other series, the method used is unclear, rendering the data somewhat open to interpretation. Moreover, the presence of tumor emboli in lymphatic spaces does not necessarily indicate the presence of a viable tumor clone capable of seeding lymph nodes or distant sites and surviving in such foreign microenvironments. Further rigorous studies are required to clearly delineate the prognostic value of both lymphatic and vascular invasion in contemporary management of head and neck squamous cell carcinoma.

Invasion of large vessels such as the jugular vein is usually only seen in bulky late-stage disease.[360]

Perineural Invasion

Squamous cell carcinomas of the head and neck exhibit a high frequency of neurotropism, as do salivary gland carcinomas, in particular adenoid cystic carcinoma (Fig. 3.16).[361] Perineural invasion in the oral cavity involves reciprocal signaling between nerves and tumor cells,[362–367] stimulating increased migration ability in malignant cells. Thus, perineural invasion in squamous cell carcinoma results in both poor locoregional control[368,369] and high risk of nodal metastasis.[368] Subsequently, perineural invasion is a poor prognostic factor for survival.[335,368,370]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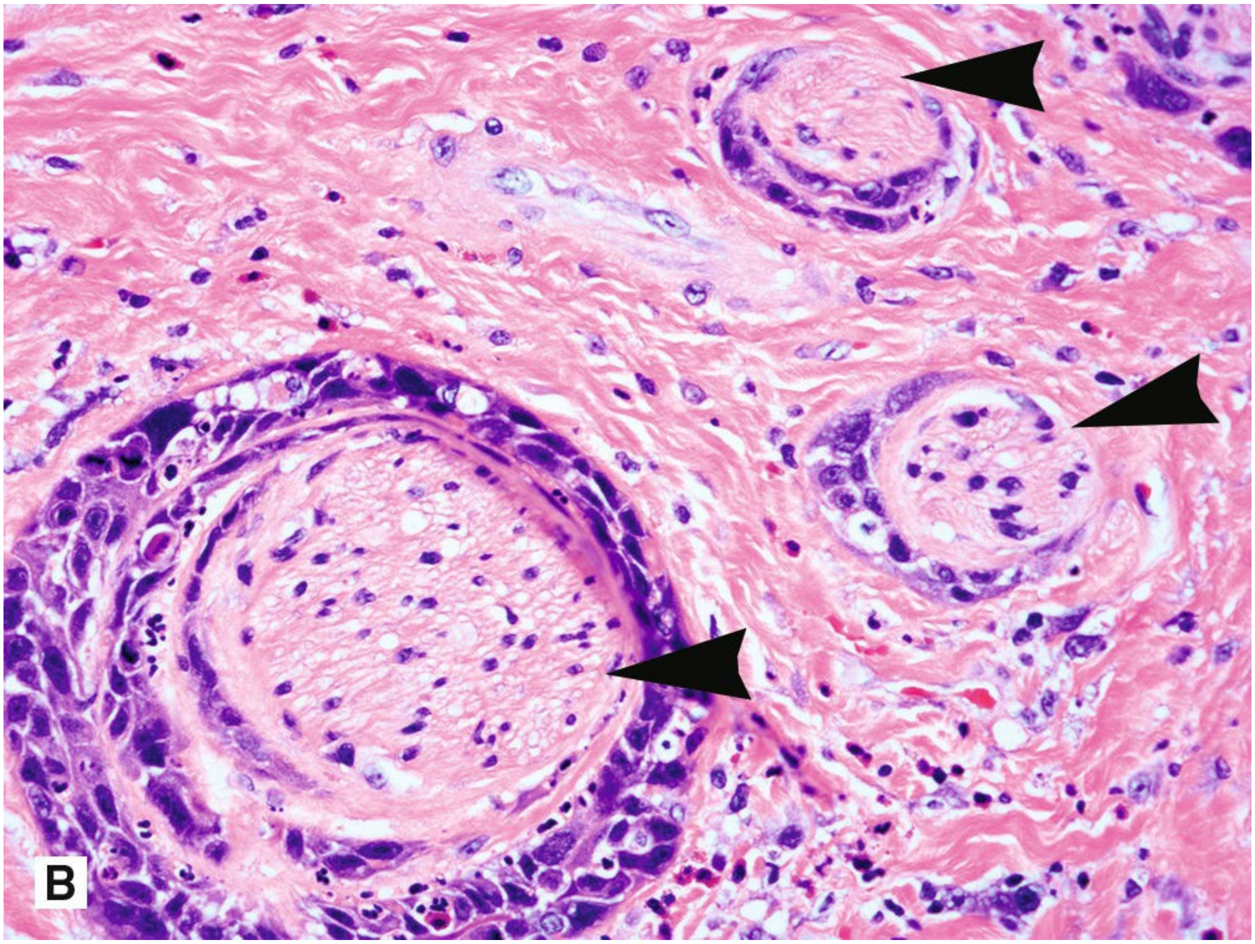

Figure 3.16 Perineural invasion in which tumor wraps around nerves is a common feature of adenoid cystic carcinoma **(A)** but can be seen in other malignant tumors including squamous cell carcinoma **(B)** (*arrowheads* detailing the nerves).

Histologically, the identification of perineural invasion requires tumor cells to be present within the nerve sheath, or demonstrate circumferential growth around at least 33% of the nerve. Entrapped nerve within tumor that does not demonstrate such evidence of neurotropism is not considered to represent perineural invasion.[371,372] It is unclear if the prognostic effects of perineural invasion depend on nerve diameter.[335,373] Extratumoral perineural invasion may portend worse outcomes.[374]

Perineural invasion is an indication for adjuvant chemoradiation therapy.[375,376] Improved outcomes after therapy may result not only from destruction of tumor cells but also from disruption of the nerve–tumor signaling microenvironment.[365]

Bone and Cartilage Invasion

Invasion of bone or cartilage by tumor is a sign of aggressive behavior and is largely associated with large primary tumors.[377–379] Whereas focal cortical erosion is common, particularly adjacent to teeth in gingival squamous cell carcinoma, only true medullary invasion is associated with local recurrence and poor survival rates, even in small tumors (Fig. 3.17).[380,381] Similarly, cartilage invasion by squamous cell carcinoma of the larynx or ear canal is historically associated with more aggressive tumors and higher rates of locoregional recurrence.[382–384]

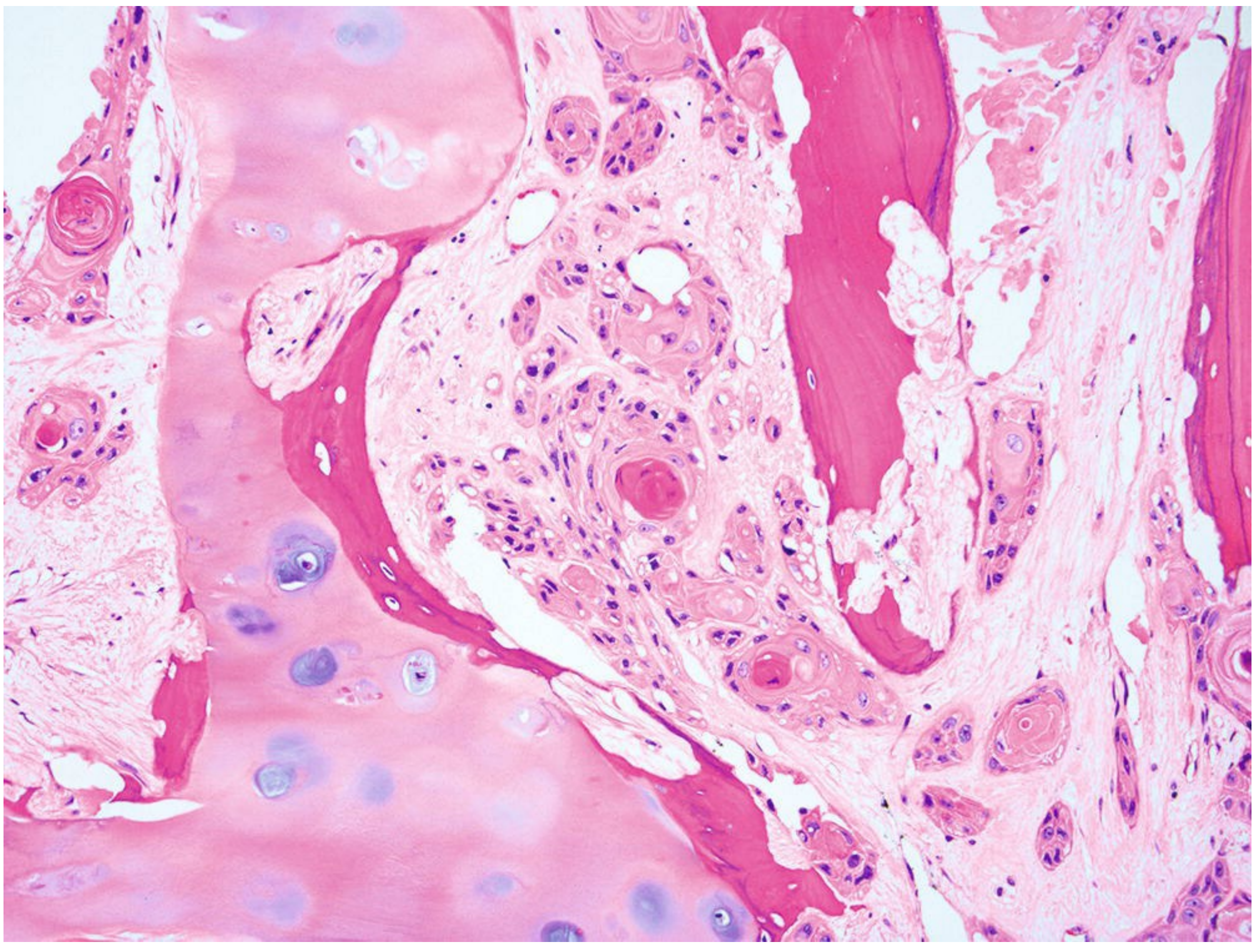

Figure 3.17 Squamous cell carcinoma invasive into the ossified cartilage of the larynx.

Margin Status

The presence of invasive carcinoma at or near surgical margins is a risk

factor for local recurrence[80,120,385–387] and worse survival.[385,388] Depending on the type of resection, resection margins include mucosal margins, soft tissues (including vascular and neural structures), and bone. Definition of what determines a positive margin can be a controversial issue, with differences of opinion on the significance of extent of involvement (R1-microscopic vs. R2-macroscopic), and what constitutes a “close” margin versus clear margins. In general practice, “close” is defined as ≤5 mm,[226] a number that does not take into account the difficult anatomy and limited resectable area of head and neck subsites.[389] In a meta-analysis of 15 publications, Alicandri-Ciufelli and coauthors[389] reported variability in the definition of close margin by anatomic subsite and procedure. Although, in general, close margins (ranging from 1 to 7 mm) were associated with local relapse to variable degrees of significance, differences in methodology and treatment modality studied limit comparability of the data.[389] The interpretation of margin status is further clouded by the presence of dysplastic epithelium or noninvasive carcinoma at the resection margin. Squamous dysplasia, in particular, is problematic as an indicator of margin status due to both poor reproducibility of diagnosis and the possibility that dysplasia represents multifocal disease, rather than a problem of local control.

In general, margins within 5 mm of lesional tissue, including dysplasia and invasive or in situ carcinoma, should be commented on,[226] and both surgeons and pathologists should be aware that in specific cases, such as squamous cell carcinoma of the larynx or oropharynx, margins as close as 2 mm may be sufficient. In other sites, including oral cavity or hypopharynx, wider margins of up to 10 mm are required to ensure clearance. Margin status should never be used in isolation to determine patient risk but is only one factor of many, including tumor stage, pattern of invasion, and use of adjuvant therapy.

Correct interpretation of “final” margin status is a collaborative effort between the surgeon and the pathologist. In all cases where margins are sent separately from the tumor, it should be clearly indicated where the tissue originated from relative to the tumor specimen, which face of the margin represents actual margin, and which surface abuts previously resected tissue. Margins are inked with dyes, which are formulated to withstand tissue-processing conditions without washing off, running, or fading. Margins are best inked and sampled as “perpendicular” or “radial” margins,

demonstrating the tumor to the inked tissue edge (Fig. 3.18). “Shave” or “*en face*” margins are inadequate for measuring distance between tumor and margin and cannot distinguish between close and wide margins. Cautery artifact at the margin distorts tissue and may render shave margins uninterpretable, whereas in radial sections, comparison between cauterized tissue and unaffected tissue further away can assist with interpretation. Proper orientation to a specimen prior to sectioning and pathologic sampling is key, and best done in person between the surgeon and the pathologist.[79] Margins may be (1) removed directly from the main resection specimen by the pathologist, (2) removed from the resection specimen and sent separately by the surgeon, or (3) taken from the patient from the in situ area of defect left after removal of the tumor.[76] Each method has advantages and disadvantages.

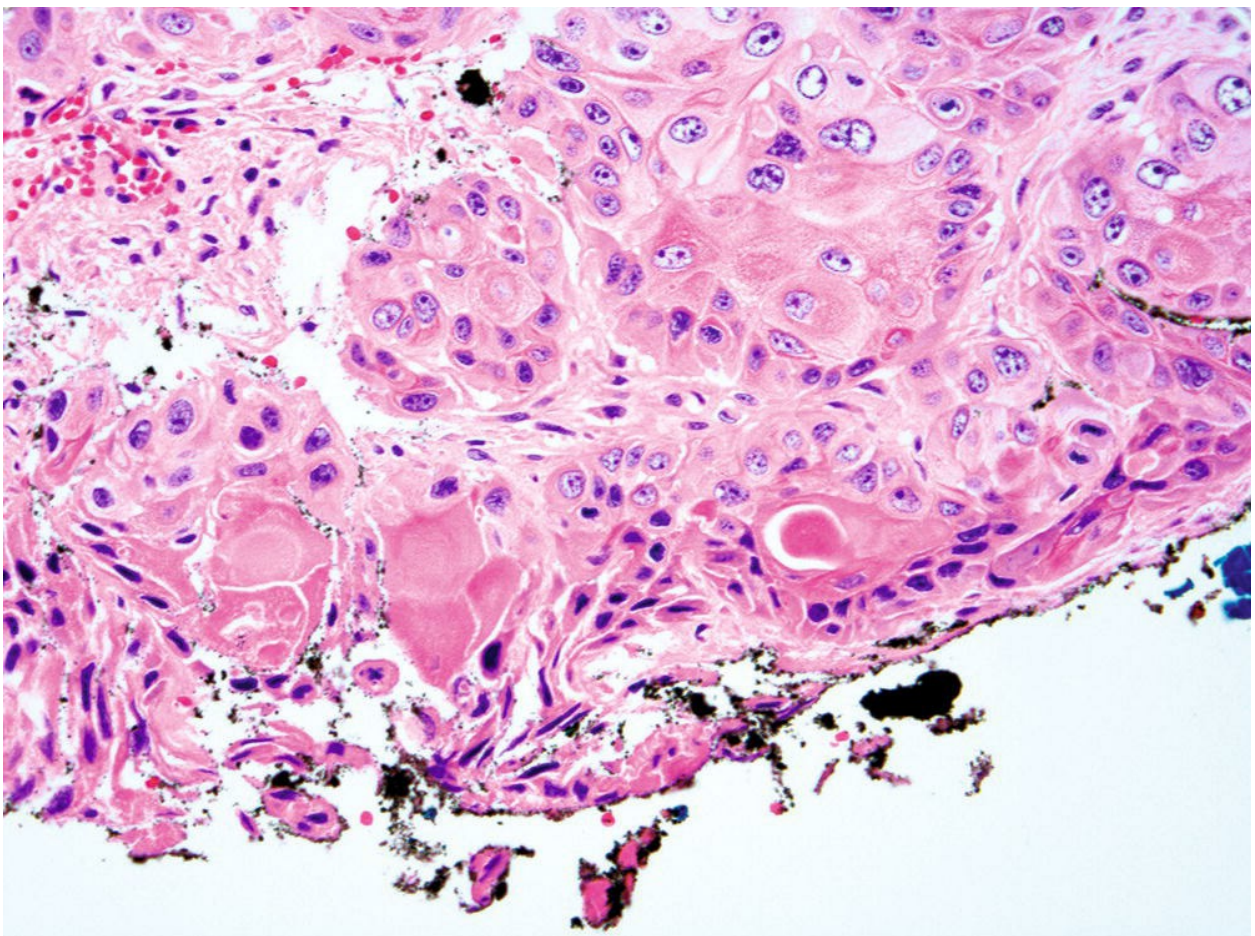

Figure 3.18 Well-differentiated squamous cell carcinoma with the tumor extending to the inked edge of the tissue specimen indicative of a positive resection margin.

In the first scenario, receipt of an intact specimen allows the pathologist to properly measure, orient, and ink the margins. In complex cases, the surgeon may wish to personally orient the pathologist to the specimen and discuss areas of particular concern. Tumor size and gross distance to all margins should be carefully measured and perpendicular sections of tumor at the closest extension to the margins selected for frozen section. This method ensures that positive margins can be precisely identified in relation to the tumor. But freezing perpendicular sections means that less of the margin can be evaluated and microscopic foci elsewhere may be missed. Specimen-removed margins sent by the surgeon are the equivalent of shave margins, and, although providing greater surface coverage, it is often unclear how they relate to the actual tumor. Removing tissue from the surgical defect as a margin produces even more difficulties in proper alignment due to tissue shrinkage and distortion.[390] Such margins are required to be taken if an initial margin is positive and should be labeled as specifically as possible (e.g., additional lateral gingival margin #1, not “additional lateral”) to provide clarity when interpreting subsequent pathology reports.

Tissue Shrinkage.

Further contributing to the margin controversy is the role of tissue shrinkage after resection and the subsequent adverse effects on measurements. In general, in situ tissue measurements and postresection measurements of oral tissues show 20% to 30% reduction.[391,392] Shrinkage begins as soon as the specimen is removed from the surrounding tissue and the natural tension is released. Formalin fixation and paraffin embedding further contribute to tissue shrinkage, albeit to a lesser extent than does contraction from innate tissue elasticity.[393] Pinning of specimens immediately after surgical excision can help to minimize tissue shrinkage—this must be done in the operating room, as by the time tissue reaches the pathology laboratory, the worst of the damage has already occurred.[391] Pinning of specimens, such as mucosal or tonsillar resections, is also an effective way to prevent curling of the margins during fixation and allows a more accurate gross measurement of tumor to margins.

Molecular Biology and Margin Assessment.

Molecular margin assessment relies on the concept of field cancerization (discussed below). If molecular alterations indicative of DNA damage are

present within morphologically “normal” epithelial cells, these are thought to be signs of a premalignant state and are associated with high risk of local disease relapse,[79] likely through the development of a second primary tumor. Molecular margin evaluation has not been shown to be relevant in HPV-associated carcinoma, and the technique remains primarily of preclinical investigative relevance.

Dysplasia

Mucosal intraepithelial dysplasia can be classified as keratinizing or nonkeratinizing, with keratinizing dysplasias being the more common of the two in the head and neck. Grading of head neck dysplasias is modeled on grading of intraepithelial neoplasias of the uterine cervix. However, this scheme does not translate well to grading of head and neck keratinizing dysplasias or take into account the propensity for carcinoma of the larynx to develop even in the absence of full-thickness dysplasia.[394] As a result, diagnostic reproducibility of head and neck squamous dysplasia is poor, particularly in three grade scales (mild, moderate, and severe).[395] Moreover, there is no significant difference for risk of invasive carcinomas between dysplasias graded as moderate, severe, or carcinoma in situ,[395] particularly as dysplasias lacking full-thickness epithelial atypia in this site may still develop invasive carcinoma (Fig. 3.19).

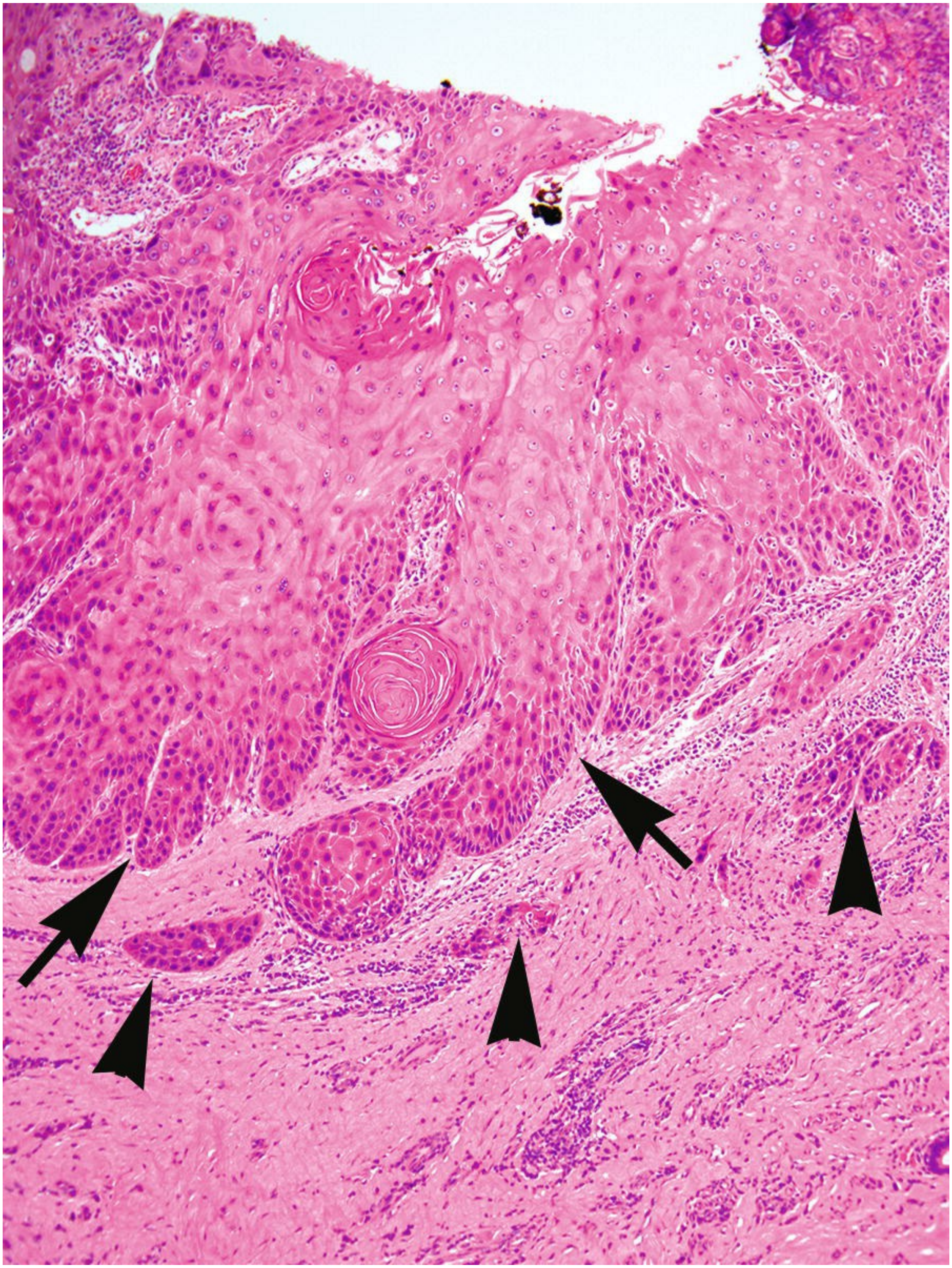

Figure 3.19 Keratinizing dysplasia, high-grade, with invasive carcinoma.

The dysplastic changes are limited to the lower (basal) zone epithelium (*arrows*) without full-thickness intraepithelial dysplasia but gives rise to nests of invasive carcinoma (*arrowheads*).

Because even moderate dysplasia carries a significant risk for development of invasive carcinoma, surgical intervention is warranted for both diagnostic and therapeutic reasons. When present at resection margins of surgical specimens, squamous dysplasias are best considered to represent positive margins, with inherent risk for local recurrence.

Microinvasive carcinoma, arising either in continuity with carcinoma in situ or directly from the base of histologically benign epithelium, represents a malignant lesion with outcomes similar to that of carcinoma in situ/high-grade dysplasia in the glottis.[396,397] In the supraglottis, microinvasive carcinoma may metastasize in up to 20% of cases, likely due to a higher concentration of readily accessible lymphatic channels subjacent to the mucosa in this region.[398]

Multiple Malignancies

Patients with an index head and neck malignancy have an increased risk of developing a second primary malignancy, with standardized incidence ratio of 2.2.[399] Etiologies include iatrogenic tumors induced as a secondary consequence of chemotherapy and/or radiotherapy, genetic predisposition, aging, and environmental carcinogens (e.g., smoking, heavy alcohol use).[400] The majority of second primary tumors are situated in the upper aerodigestive tract or may commonly arise in the lungs and more distal digestive tract.[401–406] Because the presence of a second primary tumor affects treatment approach and patient prognosis, panendoscopy or PET–CT to assess for multifocal disease is required prior to initiating therapy.

Continued smoking after treatment for the first primary tumor results in an elevated risk of developing a second primary tumor,[403] with annual incidence rates of 4.2% reported for the development of a second primary tumor, nearly 1.5 times the risk of those who quit smoking, and twice the risk of never smokers.[407] These findings underscore the importance of lifestyle modification in the treatment of head and neck carcinoma. Overall survival rates are reduced nearly 25% at 5 years after the development of second

primary malignancy,[408,409] with tumors of the lung or esophagus historically portending significantly foreshortened survival.[403]

Field Cancerization.

Multiple primary tissues may present concurrently (synchronous) or separated by a period of time (metachronous). Tumors that arise within 6 months of identification of the index primary tumor are generally considered to be synchronous, whereas those arising later than 6 months are defined as metachronous. Simultaneous primary squamous cell carcinomas of the keratinizing type have been described in 10% to 20% of cases,[401,405] whereas metachronous tumors arise in 20% to 30%.[400] In both instances, second primaries are mostly commonly thought to be associated with widespread cellular damage to the upper aerodigestive tract, a concept known as field cancerization.[410]

The theory of field cancerization proposes that DNA damage and premalignant molecular alterations do not only occur in a single cell that eventually gives rise to carcinoma as an isolated clonal event. Instead, it is thought that toxins such as alcohol or tobacco smoke, or repetitive injury from chronic inflammation and oxidative stress damage scattered cells throughout the affected mucosa.[410] These tracts of damaged cells may then give rise to multiple different neoplastic clones. Histopathologic assessment can discern damage in the form of epithelial dysplasia. However, not all altered cells may be apparent at the level of conventional H&E sections.[411] Immunohistochemical studies and molecular based techniques to detect common regulatory abnormalities associated with DNA-damaged cells (TP53 mutation, loss of heterozygosity, promoter methylation, or eIF4E overexpression) may predict local recurrence in such cases.[412–416]

Role of Immunocompromise in Multiple Malignancies.

Carcinoma is increasingly being recognized as a disease reflective of the failure of immune surveillance to eradicate altered cells. As discussed previously, patients who have squamous cell carcinoma with a healthy immune response in the form of tumor infiltrating lymphocytes have improved outcomes compared to those without. As a corollary to this, immunocompromised patients are at higher risk for development of carcinoma. Viral-associated carcinomas exemplify this risk. Merkel cell

carcinoma is often seen as a second malignancy in patients with an underlying lymphoma, particularly CLL/SLL.[417]–[419] Oropharyngeal HPV-associated squamous cell carcinoma, while being associated with very low rates of subsequent second malignancy,[399] may develop secondarily to immunocompromise—usually due to solid organ transplant[420]–[422] and potentially secondarily to chemoradiotherapy. Nonviral associated carcinomas of the oral cavity have also been reported to arise secondary to chemotherapy for ovarian cancer in patients with no other known risk factors.[423]

Ancillary Studies (Pathologic Toolbox) and Applications

Ancillary studies were developed to help elucidate diagnosis in cases where tumor histogenesis was not apparent on routine H&E-stained sections under light microscopy. Because proper therapy and clinical management require knowledge of specific tumor type, histochemical and immunohistochemical studies, along with electron microscopy techniques, were developed that could impart additional information as to the makeup of tissue and cellular components. Over the years, the understanding of the molecular basis for diseases of the head and neck has increased dramatically. Better understanding of the genomic, genetic, epigenetic, and proteomic alterations contributing to disease have come hand in hand with innovations in available technologies for evaluating underlying cellular alterations. Molecular and immunohistochemical findings are now able to guide diagnosis and can suggest targeted therapies for the treatment of malignancy based on identification of specific signaling pathway alterations. This section briefly reviews the diagnostic toolbox available to the modern pathologist, with examples of how these techniques contribute to clinical care.

Histochemical Stains

Histochemical stains are one of the oldest tools used by pathologists to analyze the components of tissue present in paraffin section. Hematoxylin and eosin, the routine stains for initial tissue evaluation, are histochemical

stains with affinity for negatively and positively charged tissue components, respectively. Other stains have varying degrees of specificity for both endogenous and exogenous compounds. Some stains detect particular chemical compounds (e.g., mucicarmine for epithelial mucins, iron stain, or melanin stain), whereas others are used for identification of microorganisms (Gram, Grocott-Gomori methanamine silver, Periodic acid Schiff [PAS], Ziehl-Neelsen, etc.) due to their affinity for complex carbohydrates or peptides seen in bacterial or fungal capsules. Others may be used to elucidate components of extracellular matrix, including reticulin, elastic stain, or Alcian blue (connective tissue mucins).[74] Prior to the era of immunohistochemistry, knowledge of tissue chemistry and appropriate application of histochemical stains were of vital importance in narrowing differential diagnoses and determining cellular makeup. Today, histochemical studies remain important in evaluation of inflammatory and infectious conditions, as well as playing a supportive role in diagnosis of a few neoplasms.

Immunohistochemistry

Immunohistochemistry relies on the detection of specific peptide antigens to discriminate between cell types, or to identify the presence of infectious agents. Although immunohistochemical staining techniques were developed in the 1970s, it was not until the late 1980s that the use of immunohistochemistry as a routine diagnostic technique in pathology became an important tool.[424]

Indirect immunohistochemical studies are based on antibody recognition of specific protein epitopes by polyclonal or monoclonal antibodies (derived from the serum of animals injected with the epitope in question or from the supernatant of in vitro hybridoma cultures, respectively). A secondary antibody conjugated to an enzyme is then used to recognize the FC region of the specific primary antibody, and the slide is incubated with the enzyme substrate, leading to a color reaction for visual detection of the presence of the epitope in question.[425]

Traditionally, immunohistochemistry has been used as an ancillary diagnostic study to distinguish the cell lineage (e.g., distinction of poorly differentiated squamous cell carcinoma from adenocarcinoma), site of origin (e.g., primary salivary gland adenocarcinoma, from metastatic

adenocarcinoma), or tumor subtype (e.g., intestinal type vs. nonintestinal type sinonasal adenocarcinoma).

More recently, immunophenotyping has been used to elucidate activation patterns of cell signaling pathways in carcinogenesis, by demonstrating altered expression of critical regulatory component, such as PTEN loss in oral[426] or thyroid carcinoma.[427,428] Although pathway expression studies reveal molecular alterations that are not entirely specific to one type of carcinoma, these analyses are increasingly important for theranostic purposes. For instance, membranous overexpression of the receptor tyrosine kinase Her-2 in salivary ductal adenocarcinoma is an indication that a patient may respond favorably to targeted therapy with trastuzumab.[429,430]

Immunohistochemical studies also have a role in the detection of infectious agents. Antibodies against specific pathogen-specific capsular antigens can help to elucidate the presence of viral infections, such as cytomegalovirus (CMV) or polyoma virus, or may detect hard-to-visualize bacteria, including spirochetes. Surrogate markers may also be used to assist the diagnosis of neoplasia and infection, and reflect changes in expression of endogenous proteins as a consequence of infection or oncogenic processes. Perhaps the most well known surrogate marker in diagnosis of head and neck cancer is $p16^{INK4a}$, the overexpression of which indicates HPV infection in oropharyngeal carcinoma. Care must be taken in the interpretation of such indirect biomarkers. P16 is a regulatory component in RB-mediated G1 cell cycle checkpoint signaling.[431] Both RB and p16 are negative regulators that function to inhibit cell cycle progression. When RB is down-regulated by exogenous viral proteins, p16 is reflexively up-regulated in an attempt to maintain homeostasis. However, p16 may be up-regulated in other contexts unrelated to viral infection, including both inflammatory conditions and other neoplastic contexts.

Technical issues in the performance of immunohistochemical studies may result in false-negative or false-positive results. False negatives commonly derive from the use of expired, degraded antibody, chromogen substrate, or other reagents; failure to perform adequate or appropriate antigen retrieval; tissue degradation; or inappropriate antibody incubation conditions, among other issues. False-positive studies most frequently result from failure to block endogenous tissue enzymatic activity and nonspecific interactions of antibody with other protein epitopes (often due to overly high concentrations

of antibody or inadequately stringent hybridization or wash conditions). In small laboratories, immunohistochemical studies are largely be performed by hand, resulting in greater variability of results from one run to the next and longer turnaround times. Large facilities with high volume of cases usually rely on automated staining machines for the majority of antibodies, resulting in greater standardization and more rapid processing.[432]

Thus, due to both technical and biologic reasons, there are inherent limitations in the interpretation of immunohistochemical studies. Furthermore, diagnostic utility of immunohistochemical studies is highly dependent on the experience of both the person performing the technical aspects of the study as well as the person interpreting the results. Interpretative errors can result from failure to recognize when a stain is technically faulty, lack of understanding of the appropriate subcellular localization of the antigen of interest, or, more commonly, from interpretive bias.[433] Interpretive bias results from assumptions made when selecting and interpreting antibody panels and from incomplete understanding of the specificity/sensitivity of the selected study for the diagnosis in question. One of the most frequent pitfalls in interpretation of immunohistochemical study is the evaluation of a single immunohistochemical study in isolation. No one antigen is ever 100% specific or sensitive for a diagnosis, and results must always be interpreted both within the context of tumor morphology and as part of an inclusionary and exclusionary diagnostic antibody panel. For instance, p63, a member of the TP53 family of transcription factors, is commonly expressed in stratified epithelium and basal cells of certain glandular structures.[434] In the head and neck, p63 is frequently used to diagnose poorly differentiated squamous cell carcinomas from salivary gland carcinoma or spindle cell squamous cell carcinoma from sarcoma. However, p63 is also expressed in salivary gland neoplasms with basal or myoepithelial differentiation, including mucoepidermoid carcinoma[435] and clear cell carcinoma[146] and may be rarely expressed in some spindle cell sarcomas.[436] Thus, expression of p63 alone is insufficient to render a specific diagnosis of squamous cell carcinoma.

One technique for minimizing subjective interpretive bias is the use of computer-assisted quantitative analysis. This method of immunohistochemical analysis is primarily used for tumors where quantification of a particular marker (e.g., KI-67 [Mib1], HER2, or TP53) has

prognostic or theranostic importance. Computer-assisted quantitative analysis has equal or improved reproducibility and accuracy compared to visual semiquantitative analysis for a variety of biomarkers.[437–439] In practice, however, the use of computer-assisted immunohistochemical analysis has not caught on widely, due to both preanalytic technical issues in staining reproducibility from case to case and analytic factors such the labor required to appropriately train the program.[440]

Electron Microscopy

Transmission electron microscopy (EM) is mainly utilized in pathology to evaluate cellular ultrastructure. Very thin tissue sections (<100 nm) embedded in a plastic polymer matrix are stained with heavy metals. A fine electron beam is then passed through the section, with the heavy metals impeding the beam due to their high density. This differential electron transmission is then detected on a fluorescent screen, which is magnified by a microscope for viewing.[441] EM revolutionized microscopy when it was first introduced in the 1950s and was responsible for much of the current understanding of the structure of cells and their component organelles, as well as for the detection and characterization of infectious disease, particularly viruses. However, since the advent of diagnostic immunohistochemistry and molecular testing, it has fallen out of favor in routine diagnostic practice, except in a few specialized situations. In the head and neck, EM is most frequently used in the evaluation of ciliary dyskinesia, a disease resulting from structural defects in proteins constituting motile cilia. Motile cilia are found in cells lining the respiratory tract, middle ear, fallopian tube, and sperm flagella. In the respiratory tract, cells with motile cilia are responsible for clearing mucus, and defective motility result in mucus accumulation and increased risk of respiratory tract infection.[442]

EM also continues to serve an important role in diagnosis of poorly differentiated tumors. Whereas immunohistochemical studies must be selected by the pathologist, and may be limited by minimal antigen expression, EM requires no a priori input and is therefore unbiased by preconceived inclusionary and exclusionary criteria. EM can distinguish, based on the presence of very few cells, squamous lineage (possessing desmosomes and bundles of cytoplasmic keratin filaments) from adenocarcinoma (short luminal microvilli), or melanoma (melanosomes), or

poorly differentiated neuroendocrine tumor (dense core granules).[441]

EM may be performed on either tissue specimens or on cytologic aspirates. Optimally, fresh tissue, no more than 1 mm in diameter, or cellular aspirate material is directly fixed in glutaraldehyde. EM can be performed on tissue removed from FFPE tissue blocks; however, ultrastructural preservation in such situations is often suboptimal.

Flow Cytometry

The use of flow cytometry in modern diagnostic surgical pathology is largely limited to the evaluation of hematolymphoid proliferations. Intact cells from fluid tumor aspirate, solid tumor aspirates, or fresh tissue biopsies are disaggregated and labeled with multiple fluorescent-tagged antibodies to specific immune antigens. Individual cells are then passed through a laser light source, allowing the detection of antigen coexpression on each cell. While detection and image analysis technologies once limited the number of antigens detectable in one reaction to four, modern technologies are enabling increasingly multiplexed reaction and detection assays.[443] Although flow cytometry can be quite sensitive, it is vital to provide appropriate clinical history so that appropriate antibody panels may be selected. In a patient with, for example, a history of a myeloid leukemia and a new mass in the neck, a panel with myeloid markers would be required to exclude myeloid sarcoma, whereas in most cases with only a history of “mass in the neck,” only a standard lymphoid panel for B-cell neoplasia is required. Flow cytometry is insensitive to detection of rare events, such as the small clonal population seen in Hodgkin lymphoma, and may result in false negatives for large cell lymphomas, due to cell fragility and propensity to lyse during specimen preparation and analysis.[444–446]

Flow cytometry may also be used on disaggregated nuclei from fresh or FFPE tissues to analyze DNA ploidy and fraction of cells undergoing DNA replication (S-phase).[447] Although several studies suggested that aneuploidy may be diagnostically[448,449] or prognostically[450] relevant in malignancy, aneuploidy may also be seen in benign neoplasms and represents a finding of uncertain significance in that context.[451] With advances in molecular diagnostics more precisely able to detect specific alterations at the DNA level, flow cytometric analysis of ploidy as a diagnostic technique has fallen

out of favor and remains largely a historical footnote.

Molecular Diagnostics

Molecular pathology is one of the most rapidly expanding disciplines within diagnostic pathology. Technically, molecular pathology is the study of disease via examination of subcellular factors, including proteins, DNA, RNA, and small molecules. Broadly interpreted, molecular pathology incorporates all facets of pathology, from the simplest histochemical stain to identifying the most complex posttranslational protein modifications by mass spectrometry. In common usage, however, molecular pathology as a discipline began with attempts to understand the genome structure and nucleotide alterations characteristic of disease (genomics and genetics). Since then, it has expanded to include gene expression profiling and proteomics, as well as investigations of regulatory mechanisms, such as miRNA, epigenetics, and posttranslational modifications, to name a few. Although many of the newer techniques pioneered in molecular pathology remain confined to the research setting, their contribution to understanding of disease pathogenesis may be rapidly translated to the clinical setting in the coming years.

Karyotype

The gold standard of classical cytogenetic analysis of chromosome number (ploidy) and structure is the metaphase karyotype. Tumor cells are taken from fresh pathology specimens and cultured in vitro. Dividing cells are then harvested and lysed to yield condensed metaphase chromosomes, the structure of which is visualized using partial enzymatic digestion and histochemical staining (typically with Giemsa stain). Such staining results in reproducible banding patterns unique to each chromosome pair. At best, conventional karyotypic banding may detect genomic alterations on a 1.5-megabase scale and typically has an average resolution of 7 to 10 megabases.[452] Due to this low resolution, small “cryptic” genomic alterations are undetectable by conventional karyotyping. Moreover, the source of genetic material in complex rearrangements and extraneous marker chromosomes may be impossible to identify. Further limiting the utility of karyotype is the difficulty in culturing tumor cells, which may not grow well under in vitro conditions or which may be overgrown by normal stromal

cells.

Cytogenetic studies have shown that genomic alterations are common in keratinizing squamous cell carcinoma of the head and neck, in particular losses of 3q, 5q, 7p, 8p, and 9p.[453,454] Although insufficiently specific for diagnostic purposes, such alterations were historically used to map chromosomal loci of tumor suppressor genes. Karyotypic studies are valuable in diagnosis of hematolymphoid malignancies and soft tissue sarcomas, both of which frequently possess characteristic chromosomal rearrangements,[455,456] and have the potential to be useful in other tumor types with characteristic translocations, including salivary gland carcinomas.

In Situ Hybridization

In situ hybridization (ISH) is a technique for visualizing specific DNA or RNA sequences present within cells of interest. Compared to conventional karyotype analysis, ISH has the dual advantages of increased speed and flexibility as to tissue preparation. Where karyotyping may require weeks for tumor cells to grow, ISH may be performed in a matter of days. With appropriate procedural modifications, ISH may be performed on frozen tissue sections, standard FFPE, or cytology aspirates and smears. Metaphase chromosomes are not required. Another advantage of ISH is that when intact tissue sections are used, it is possible to more accurately localize lesional tissue for evaluation.

ISH is performed using chromogen-labeled nucleotide probes complementary to specific sequences of interest. Probes [from 250 to 1,500 base pairs in length for RNA chromogenic ISH (CISH) to 50 to 500 kilobases for fluorescence ISH] cannot be used to detect single base pair mutations. Tissue sections or disaggregated tissue nuclei are treated to permeabilize cellular and nuclear membranes to the probe and then heated to denature nucleic acids. The probe is then added and allowed to anneal to the tissue DNA. After washing to remove excess probe and nonspecific interactions, the chromogen can be visualized by cytochemical stain (conventional ISH) or by fluorescence microscopy (fluorescence ISH). Unlike karyotypic analysis, ISH requires some a priori knowledge as to the abnormality that one is expecting to find. Probes are generated to specific sequences, and it is up to the treating team to convey necessary clinical information that along with histopathologic features will enable pathologists to select the most

appropriate test.

Chromogenic In Situ Hybridization.

CISH has long been used in the head and neck for the detection of pathogenic (viral) DNA. Nucleotide probes against specific DNA or RNA sequences are conjugated with an enzyme and incubated directly on permeabilized, denatured tissue sections and allowed to bind to complementary sequence within the tissue. After washing away excess and nonspecifically bound probe, the slide is incubated with colorimetric enzyme substrate to generate colored signal in order to visualize hybridized probe.[457] Because normal cells only have two alleles that may bind the probe, and it requires many enzymatic reactions to generate visible color, CISH is generally too insensitive for detection of small DNA mutations or deletions. Viral infection generates many copies of the viral genome or mRNA within an infected cell and is therefore readily detectable.[457] ISH for kappa and lambda light chain mRNA is also sometimes used in place of immunohistochemistry to type plasma cells neoplasms but lacks sensitivity.[458]

In the head and neck, the use of ISH to detect Epstein-Barr–encoded RNA (EBER) has proved invaluable in diagnosis of nonkeratinizing NPCs and lymphomas. HPV ISH for detection of high-risk versus low-risk HPV infections is widely used but is less sensitive or specific than PCR-based detection methods (discussed below).[121]

Fluorescence In Situ Hybridization.

Until recently, fluorescence in situ hybridization (FISH) was not considered a routine part of the diagnostic arsenal for tumors of the head and neck. Whereas the utility of conventional ISH is limited by the low resolution of the cytochemical chromogen, FISH is characterized by a relatively high resolution and, like conventional karyotypic analysis, is mainly used to identify the presence of alterations of genomic copy number or structure. The most commonly used FISH probe sets are locus/centromeric probes and break-apart probes. A third probe set, fusion probes, are less frequently seen in clinical practice.

Locus/centromeric probes function to enumerate copy number alterations of specific gene loci. The probe set involves two probes, one to the gene locus of interest and a second to the centromere of the chromosome the gene

is normally situated on. Each probe is tagged with a different color fluorescent chromophore to distinguish them from one another. The number of signals of the gene locus are counted and tabulated against the number of centromeric signals. In a normal cell, the ratio between target and centromere is 1–2:1 depending on if the cell is undergoing DNA replication. Thus, the centromeric probe acts as a control to normalize for aneuploidy (aberrant chromosome copy number) and tissue sectioning artifact. In the head and neck, locus/centromeric probes are most commonly used to evaluate for the presence of high-level *HER2* amplification in salivary ductal carcinoma, with low copy number increase and high-level amplification generally considered as target:centromere signal ratio ≥2 and ≥9 to 10, respectively.[459,460]

Break-apart probes consist of a set of probes designed to flank a specific gene or chromosomal locus of interest. As with locus/centromeric probes, each probe is tagged with a different fluorescent chromophore, typically green and orange. In a normal chromosome, the signals are juxtaposed such that they appear as a single yellow dot (due to spectral overlap) or as closely apposed green and orange dots. If a chromosomal translocation occurs such that the breakpoint lies in the region flanked by the probes, the signals become visualized as spatially distinct dots.

In recent years, a number of characteristic gene translocations have been identified in tumors of the salivary gland (Table 3.6), the existence of which has begun to transform diagnostic criteria. For instance, (hyalinizing) clear cell carcinoma of the salivary gland, first described in 1994,[461] was, until a few years ago, considered to be a diagnosis of exclusion, representing a “wastebasket” term for a heterogenous group of tumors. Recently salivary gland clear cell carcinomas were found to have a specific *EWSR1-ATF1* translocation in over 90% of cases,[146] whereas other salivary tumors lacked this gene rearrangement.[148] Thus, for the first time, clear cell carcinoma was proven to be a distinct entity. Similarly, identification of a characteristic *ETV6-NTRK3* translocation finally allowed mammary analogue secretory carcinoma, long misdiagnosed as a zymogen granule–poor form of acinic cell carcinoma, to be recognized as a distinct entity.[462,463] The therapeutic and prognostic implications of these subtypes are still being investigated. Nevertheless, FISH has now become an integral part of the workup for salivary gland neoplasia.

Thyroid malignancies also harbor recurrent translocations, albeit at lower

frequency than do *RAS* or *BRAF* point mutations, with *RET/PTC* rearrangements present in ~20% of papillary carcinoma and *PAX8-PPARγ* fusions in 35% of follicular carcinomas and a limited number of follicular adenomas, NIFTPs, and FVPTCs (Table 3.7).[176] Unfortunately, the relative infrequency of these fusions and the diverse array of *RET* family members involved, as well as limited data as to their prognostic significance, largely precludes utility of diagnostic FISH tests for these rearrangements.

With both enumerative and break-apart FISH probes, analysis of FISH performed on 4-μm paraffin section requires signal evaluation in between 100 and 200 tumor nuclei for accurate interpretation, although in some circumstances, such as very small biopsies, 50 may be used. High numbers of nuclei are evaluated to compensate for technical factors such as sectioning artifact or contamination of counts by nonneoplastic stromal or inflammatory cells. True quantitative analysis is not possible.

The use of disaggregated tumor nuclei for FISH, although technically more challenging, does allow for signal number quantitation, although contamination by nontumor cells poses a higher risk than on paraffin section. The use of disaggregated nuclei for FISH is primarily a consideration when precise distinctions must be made as to the cutoff for gene locus amplification. FISH is also susceptible to false-negative results and technical failures due to nucleotide degradation during processing and may not yield results in cases that have undergone over- or underfixation or that have been subjected to decalcification.

Spectral Karyotyping.

Spectral karyotyping (SKY) is a form of FISH that may be used to more precisely identify chromosome of origin in complex karyotypes. An array of chromosome-specific nucleotide probes, each tagged with different fluorescent chromogens, are hybridized to a metaphase preparation, thereby "painting" components of each chromosome in a different color.[464] This technique may identify small insertions and can be used to resolve complex rearrangements, but its use in clinical practice is limited by technical difficulties in performing and interpreting the study.

Polymerase Chain Reaction

Polymerase chain reaction (PCR)–based techniques offer a higher resolution

look at nucleotide sequence abnormalities than does either karyotyping or ISH. PCR is a highly flexible technique that may be performed on genomic DNA or RNA transcripts [reverse transcriptase–PCR (RT–PCR)] and has been incorporated into a variety of assays to detect the presence of infectious pathogens, genetic point mutations, deletions, chromosomal rearrangements (including cryptic insertions, inversions, and translocation), and even epigenetic silencing via promoter methylation. PCR-based reactions are also the foundation for second- and third-generation sequencing technologies.

Real-time (quantitative) PCR (Q-PCR and QRT-PCR) is an improvement on traditional, semiquantitative PCR. QPCR uses a system of paired fluorescent chromophore and quencher molecules for detection of PCR products after each cycle of amplification. Upon successful amplification, fluorescent chromophores associated with either primers or sequence-specific probes for the amplicon of interest are dissociated from the quencher, and quantitation of transcript number is performed via analysis of fluorescence intensity.[465] QPCR has the advantage over conventional PCR of more accurate quantitation, high sensitivity, and the ability to multiplex reactions, using differently colored chromophores. These advantages have made QPCR the preferred platform for both research and clinical diagnostics.[466]

RT–PCR is sometimes used to detect chromosomal translocations in mRNA transcripts. However, its use in this context is limited by the requirement that both of the translocation partners and their respective breakpoints be known. This technique is not broadly implemented in the clinical diagnosis of head and neck carcinoma, in part because recurrent fusions are still being elucidated in epithelial neoplasia, and fusion partners and their frequencies are as yet poorly understood, and in part due to technical limitations of working with severely fragmented transcripts. In most cases, RT–PCR performed on FFPE tissues is ideally designed for a transcript of 150 base pairs or less and a maximum of 300 base pairs.

PCR offers improved sensitivity to ISH for the presence of exogenous DNA or genetic mutations, due to the target sequence amplification process inherent to PCR. Thus, PCR is an ideal technique for small biopsies or when only scant DNA or RNA can be retrieved. Care must be taken to avoid cross- and carry-over contamination from other specimens being processed. Preanalytic factors also play a role in the success of PCR. Tissue degradation begins at the moment of surgery with ischemic changes. Both DNAses and

RNAses are active in tissue, and unfixed specimens at room temperature do have measurable declines in the amount and quality of retrievable nucleotides. Specimen processing in formalin results in further degradation and fragmentation, with RNA being the most susceptible. Decalcification, which often relies on strong acids, may further degrade nucleotide quality.

PCR-based techniques are sometimes used as ancillary studies in the diagnosis of thyroid nodules with indeterminate cytology on FNA biopsy (Bethesda class 3–5). *BRAF* mutations (n.T1799A, p.V600E) are relatively specific to papillary carcinoma and are not present in benign lesions, whereas *NRAS* or *HRAS* mutations (most commonly codon 61) are more common in follicular pattern lesions (including follicular variant of papillary carcinoma, NIFTP, and follicular carcinoma, as well as, less frequently, follicular adenoma.)[173] The regions of interest harboring possible mutation are readily amplified by PCR, and wild-type and mutant alleles are then detected by melting curve analyses and/or Sanger sequencing. *BRAF* mutational testing has variable sensitivity for PTC, with detection rates as low as 39% and accuracy from 69% when applied to all tumors classified as Bethesda 3–5.[467,468] When testing is limited to Bethesda 3 lesions only, the sensitivity drops to 14%.[467] Limiting testing to indeterminate lesions (Bethesda 3 and 5) improves sensitivity to 80% when combined with cytologic findings.[469] The specificity of *BRAF* mutation for malignancy is >99%.[468–470]

Combined testing for a panel of mutations, including PCR for *BRAF*, and *RAS* mutations and FISH for *RET/PTC* and *PAX8/PPARγ* rearrangements, offers improved sensitivity for malignancy, at the cost of specificity, with ~87% of cases with mutations subsequently being shown to be histologically malignant. In contrast, approximately 6% to 28% of mutation-negative nodules were ultimately malignant, depending on whether lesions had been previously classed as Bethesda 3, 4, or 5.[471]

In some institutions, PCR has supplanted ISH as a more reliable test for detection and genotyping of HPV viral infection in oropharyngeal squamous cell carcinoma. To screen for the presence of high-risk HPV, consensus primers are chosen that will amplify a high number of different HPV genotypes. Target sequences are conserved regions of the HPV genome such as the gene for the L1 capsid protein.[472,473] In cases that test positive for high-risk HPV, the specific genotype can then be identified using either

direct sequencing or secondary genotype-specific PCR (often performed with QPCR and primers to the L1 or E6/E7 regions of the HPV genome, as a multiplexed reaction), among a variety of other techniques.[474]–[476] These tests have high sensitivity for detection of HPV.[121]

Array-Based Technologies

Newer technologies in nucleotide analysis are based on the principle of massively parallel processing of short fragments of DNA/RNA followed by computational analysis with reference to a source database to identify quantitative or sequence variations.

Array-based techniques such as array comparative genomic hybridization (array CGH) and gene expression analysis (GEA) rely on a chip upon which thousands of short oligonucleotide probes are immobilized. Probes are then hybridized to fluorescently labeled nucleic acids in the analyte sample; intensity analysis of probe signal allows for quantitation of copy number of DNA or RNA (cDNA). Expression arrays are also used to assess noncoding RNAs such as microRNA (miRNA) expression profiles. CGH is performed to detect copy number variations (genomic gains or losses). Array CGH offers considerable advantages over its precursor, metaphase CGH, in that the use of a standardized array allows significantly finer detail as to the sites of copy number variations, providing resolution at the 100 to 200 kbp level (compared to 5 to 10 megabases for conventional CGH), while also offering increased sensitivity of detection.[477]

Gene expression array assays have gained popularity in clinical diagnostics for assisting risk stratification of thyroid cytology specimens with indeterminate risk of malignancy. Understanding the limitations of such techniques is critical for proper application in the clinical context. As described above, mutational analysis in indeterminate thyroid FNAs have a low sensitivity for malignancy. A gene expression classifier developed by comparing expression profiles of benign entities against those of malignant tumors was, in pilot studies, reported to have 84% specificity and sensitivity >90%.[478] In a subsequent validation series, sensitivity for malignancy was found to be 92% but specificity only 52% in indeterminate lesions.[479] In practical terms, a negative result for an indeterminate nodule has a NPV of 94%[479] and can be used to exclude malignancy, but a positive result is not

informative.

Many microarray-based gene or miRNA expression profiling studies have been reported in the head and neck literature for squamous cell carcinomas, proposing to variously improve prediction of outcomes, or for screening purposes, but these assays are not yet ready for clinical use.[480] Gene and miRNA expression profiling of saliva has also been proposed as a diagnostic and theranostic tool for inflammatory conditions such as Sjögren syndrome.[481]

Next Generation Sequencing.

There are a wide variety of second and third technologies in development or practice for sequencing of high-volume data sets (genomic, exomic, transcriptomic DNA). Most second-generation sequencing is characterized by massive throughput at relatively low cost. These technologies have led to the revolution in so-called personalized medicine in which it is now possible to analyze the entire exome of protein-coding sequences in normal or neoplastic tissue for only a few thousand dollars.[482,483] Most second-generation technologies rely on prior specimen amplification. These amplified templates are immobilized on a substrate and synchronously analyzed using a PCR-based strategy known as sequencing by synthesis. Sequencing reads are obtained using fluorescently labeled nucleotides, with serial imaging after each nucleotide addition (“wash and scan cycles”). Sequence read lengths are shorter than conventional Sanger sequencing, and computational analysis is required to align thousands of overlapping reads into complete sequences.[484] Next generation sequencing (NGS) is currently gaining in favor is some institutions for screening tumors for broad panels of actionable or diagnostic genetic or genomic alterations. Such alterations most commonly consist of point mutations or gene fusions that can readily be detected using customized probe sets for the specific regions of interest. In head and neck cancer, NGS panels are most commonly utilized for diagnosis of thyroid tumors in cytologic preparations. It should be noted that widespread adoption of NGS in pathologic diagnosis of the head and neck may be limited by prohibitive cost of validation and heavy regulatory requirements in some states.

The aim of many third-generation sequencing technologies is to provide reads at the single molecule level without a need for either an initial

amplification step or synchronized sequencing reactions. However, currently, third-generation technologies suffer from lower raw read accuracy compared with first- or second-generation sequencing, with error rates of at least 5%.[484] Technologic hurdles facing both second- and third-generation technologies include developing adequate informatic infrastructure for computation and interpretation of large, complex data sets and ensuring fidelity and relevance of results in the clinical diagnostic context.

Proteomics

Modern proteomics studies use mass spectroscopy to identify peptide fragments, which then are analyzed to reconstruct proteins present in a tissue or fluid sample. Depending on the type of mass spectroscopy performed, the expression can be quantitated or peptides assessed for posttranslational modifications such as phosphorylation or acylation. In this way, a snapshot of the actual cellular components at a given point in time can be identified. The use of proteomics as a diagnostic modality is somewhat limited in anatomic pathology, in part due to the severe alterations and damage to cellular proteins from formalin fixation and processing. However, in the research setting, proteomic analyses are beginning to gain prominence in the identification of potential druggable targets.[485]

Solid phase microarray platforms such as reverse phase protein array (RPPA) are another way to detect presence of proteins in cellular extracts. Lysates are printed, in replicate, as multiple individual spots on the microarray and then incubated with antibody against the antigen of interest. Unlike mass spectroscopy, however, the targets of interest must be determined beforehand in order to select and validate antibodies.[486] At the current time, proteomic studies are of growing interest to researchers in the field of personalized medicine but are not yet ready for application to clinical practice.

Epigenetics

Epigenetics is the study of modifications affecting the chromosome without altering DNA sequence.[487] Such modifications include silencing of gene promoters by hypermethylation, as well as modifications to chromatin conformation by posttranslational modifications to histones.[488] Studies are

conducted using a variety of molecular techniques including methylation-specific PCR, proteomics, and immunohistochemistry, among others. Epigenetic modifications are not actively studied for diagnostic purposes at the present time; however, studies are ongoing into epigenetic profiles of head and neck carcinomas,[489–493] with the hope that better understanding the effects of these alterations on gene expression will lead to improved risk assessment and therapies for these malignancies.

Conclusions

Tremendous advances have been made in the past few decades in establishing tumor diagnosis and prognosis based on histopathologic and molecular features. The ever-accelerating pace of modern medicine leads to challenges in keeping up with the latest advances in disease biology. Nevertheless, treatment planning is reliant upon tissue diagnosis, and the entire multidisciplinary team must work together to understand the implications of new findings and evolve their approach to meet new challenges. At the same time, an appreciation of the basics, including handling of the gross specimen and, in particular, evaluation of margins, cannot be overlooked, even in the molecular age.

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4 Epidemiology, Demographics/Disparity

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Cancer may involve many sites in the head and neck including the oral cavity, pharynx, larynx, salivary glands, thyroid, and sinonasal cavity. These cancers have a variety of biologic behaviors, and whereas some of these subsites share common risk factors, others do not. Smoking is a major risk factor for cancers of the oral cavity and larynx but is not considered a risk factor for cancer of the thyroid. Human papillomavirus (HPV) is a risk factor for squamous cell carcinoma of the oropharynx but not for other more common cancers of the head and neck such as larynx and thyroid. The risk factors for cancers of the head and neck vary by site (location); therefore, the incidence of cancers of the head and neck, as shown in Tables 4.1 and 4.2, varies markedly across sites, time, and gender. The risk factors, incidence, prognosis, and survival will be presented separately for each site. The discussion in this chapter is mostly confined to the United States. Information on global trends in cancer of the head and neck appears elsewhere in this book (see Chapter 25).

Table 4.1 Male Age-Adjusted Incidence by Cancer Site, 1973–2009

	1973–1989	1990–1999	2000–2009	APC 2000–2009
Oral cavity and pharynx	20.19	17.55	15.80	–0.1
Lip	3.67	2.06	1.08	–6.7[a]
Tongue	3.55	3.69	4.40	2.7[a]
Salivary gland	1.40	1.56	1.64	0.7[a]
Floor of the mouth	2.19	1.55	0.98	–3.9[a]
Gum and other mouth	1.10	0.97	0.79	–2.0[a]
Tonsil	1.83	2.00	2.59	4.0[a]
Oropharynx	0.52	0.50	0.54	0.2
Nasopharynx	1.01	1.05	0.95	–0.2
Hypopharynx	2.11	1.78	1.20	–3.3[a]
Other oral cavity and pharynx	0.64	0.62	0.31	—
Larynx	8.29	7.01	5.50	–2.3[a]
Nasal cavity and paranasal sinuses	0.80	0.66	0.57	–1.3[a]
Thyroid	2.88	3.47	5.45	5.8[a]

[a]Indicates significant change in *p*-value ($\alpha = 0.05$). Annual percent change (APC). APCs could not be calculated for some sites due to sparse data.

Table 4.2 Female Age-Adjusted Incidence by Cancer Site, 1973–2009

	1973–1989	1990–1999	2000–2009	APC 2000–2009
Oral cavity and pharynx	7.49	6.92	6.32	–0.9[a]
Lip	0.36	0.32	0.25	—
Tongue	1.57	1.57	1.71	0.4[a]
Salivary gland	0.92	0.96	1.03	0.2
Floor of the mouth	0.83	0.60	0.40	—
Gum and other mouth	0.61	0.59	0.54	–1.2[a]
Tonsil	0.74	0.61	0.56	–1.2[a]
Oropharynx	0.18	0.15	0.15	—
Nasopharynx	0.39	0.41	0.38	—
Hypopharynx	0.52	0.42	0.28	—
Other oral cavity and pharynx	0.24	0.21	0.12	—
Larynx	1.45	1.49	1.12	–2.6[a]
Nasal cavity and paranasal sinuses	0.39	0.35	0.31	—
Thyroid	6.71	8.95	15.84	6.8[a]

[a]Indicates significant change in *p*-value ($\alpha = 0.05$). Annual percent change (APC). APCs could not be calculated for some sites due to sparse data.

CANCER OF THE ORAL CAVITY AND PHARYNX

Approximately 29,620 men and 11,760 women in the United States are diagnosed each year with cancer of the oral cavity and pharynx.[1] Cancer of the oral cavity and pharynx (OCPC) includes several subsites: lip, tongue, salivary glands, floor of the mouth, gum and other mouth, nasopharynx, tonsil, oropharynx, hypopharynx and other oral cavity, and pharynx. Other oral cavity and pharynx cancers include Waldeyer ring, overlapping lesions of lip, oral cavity, and oropharynx as well as not otherwise specified (NOS) cancers. As shown in Figure 4.1, the most common type of OCPC is cancer of the tongue (28%), followed by tonsil (15%) and gum and other mouth (14%). Squamous cell carcinoma is the most common cancer (82%) of OCPCs. Other less common histopathologies include adenocarcinomas, mucoepidermoid carcinomas, as well as ductal and lobular cancers.[2]

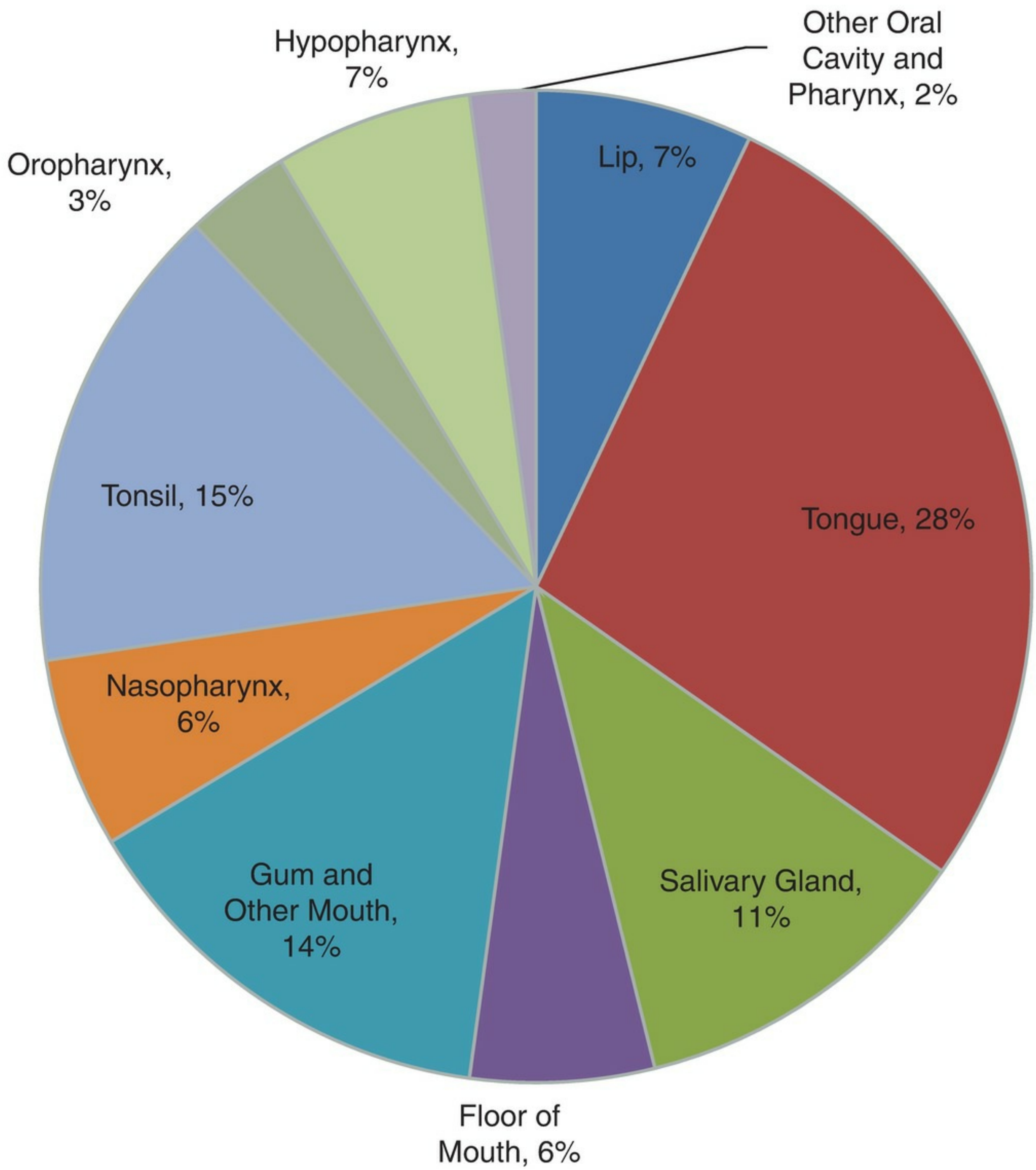

Figure 4.1. Distribution of cancer of the oral cavity and pharynx by subsite in SEER 18 2000–2009. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission.

http://www.seer.cancer.gov)

Risk Factors

The International Agency for Research on Cancer (IARC) has classified smoking tobacco as a cause of cancer of the oral cavity.[3] Studies have consistently shown an increased risk of cancer of the oral cavity and pharynx among smokers.[4–9] Case–control studies have reported up to 11 to 12 times risk of OCPC among current smokers compared to never smokers,[4,5] and the risk of OCPC increases with amount and duration of smoking.[6–9] In addition, the synergistic effect of alcohol on smoking has been established in several studies.[6,7,10] For example, among never drinkers, the odds of oral cavity and pharyngeal cancer are 1.7 to 1.9 higher for cigarette smokers, and for heavy drinkers, these odds are 9.60 to 11.37 higher.[6] There is some heterogeneity in the effect of cigarette smoking by OCPC subsite as tobacco exposure is found to be more strongly associated with cancers of the soft palate than other sites.[11] Additionally, the use of black versus blond tobacco may have an even greater risk of oral cavity and pharyngeal cancer.[12] Among former smokers, the risk of cancer of the oral cavity is less than that of smokers, and one study reported that after 10 years of quitting, former smokers had the same risk of OCPC as never smokers.[9,13]

Several forms of smokeless tobacco are associated with cancer of the oral cavity and pharynx. Smokeless tobacco in the form of snuff, which is found most commonly in the United States, is independently associated with cancer of the oral cavity and pharynx in US studies.[14] However, studies of smokeless tobacco in Sweden and Norway, where moist snuff or snus is more common, have not reported increased odds of oral or pharyngeal cancer.[15,16] Another form of chewing product called betel quid used in Asia that may or may not contain tobacco, is also associated with OCPC. IARC concluded that betel quid with tobacco causes cancer of the oral cavity and pharynx, whereas betel quid without tobacco causes cancer of the oral cavity only.[17,18]

Not only does alcohol interact with tobacco to increase the risk of cancer of the oral cavity and pharynx, but also there is an independent contribution of alcohol on OCPC.[16,19,20] Among nonsmokers, the risk of cancer of the oral cavity and pharynx is elevated among alcohol drinkers compared to

nondrinkers.[21,22] A dose–response relationship between alcohol consumption and cancer of the oral cavity and pharynx has also been observed as heavy drinkers have a particularly high risk of cancer of the oral cavity and pharynx.[10,16,19,21] A meta-analysis found a 4.6- and 6.6-fold increase in odds of cancers of the oral cavity and pharynx among heavy drinkers compared to never drinkers, respectively.[23] Some studies have suggested variations in the effect of alcohol by subsite; however, the pattern is inconsistent across studies.[10,12,24]

Although historically, cancers of the oral cavity and oropharynx have been attributed to tobacco and alcohol, in recent years, an increasing number of cases of squamous cell carcinoma, particularly those in the oropharynx, have been associated with HPV infection. Several case–control studies have demonstrated an association between HPV and the risk of squamous cell carcinoma of the head and neck, independent of tobacco and alcohol use.[25–28] A multicenter case–control study containing 1,670 cases and 1,732 controls from nine countries reported a positive association between HPV deoxyribonucleic acid (DNA) positivity in oral biopsies and oropharyngeal cancer (OR 4.9, 95% CI 2.6 to 9.1), after having been adjusted for demographic information as well as smoking and alcohol intake.[26] In the same study, the association was even stronger when the presence of high-risk HPV 16 was considered.[26] A subsequent case–control study in the United States also reported a strong association between cancer of the oropharynx and HPV oral infection (adjusted OR 14.6, 95% CI 6.3 to 36.6) as well as HPV 16 E6 and E7 positivity (OR 58.4, 95% CI 24.2 to 138.3).[27]

HPV 16 accounts for the majority of HPV-related cancers, followed by HPV-18, and even more rare are HPVs 33, 6, and 11.[26,29,30] Case series report a wide range of HPV prevalence from 4% to 80% among oral cavity squamous cell carcinoma (OCSCC) and 14% to 57% among oropharyngeal squamous cell carcinoma (OPSCC), which is likely due to variations in populations, risk factors, and HPV detection methods.[29] A pooled analysis of over 2,500 OCSCC cases across several continents including Asia, Europe, Australia, North America, and South America reported a 23.5% (95% CI 21.9 to 25.1) prevalence, whereas the prevalence of HPV positive among 969 OPSCC cases in this pooled analysis was higher (35.6%, 95% CI 32.6 to 38.7).[30] Though the aforementioned pooled study reported an overall higher

HPV positivity among North American cases of OPSCC (47%) and OSCC (16%) than the worldwide combined estimate, other multinational studies have shown no differences in HPV prevalence among OPSCC and OSCC across continents.[26]

The potential synergistic effect of tobacco, alcohol, and HPV positivity is less well understood. Several investigators have studied this issue using a variety of methods including hospital- and population-based case–control studies with incidence of cancers of the head and neck, whereas some studies included only cancers of the oropharynx. A population-based study of oral cavity and oropharyngeal cancer reported a higher prevalence of smoking in HPV-seropositive cancers (31.3%) compared to HPV-seronegative cancers (20.1%).[27] The finding of additive interaction for tobacco and HPV exposure has been observed in other studies as well.[26] However, a hospital-based case–control study found a similar proportion of smokers in HPV-positive (63%) and HPV-negative (67%) cases.[31] Similarly, other studies have found no interaction between HPV and smoking.[25,32]

Some occupational studies have found increased odds of cancer of the oral cavity and pharynx among workers exposed to aromatic amines, polycyclic aromatic hydrocarbons, solvents, and nitrosamines[33,34]; however, these associations are not consistent across studies and some studies were unable to control for tobacco use. Consumption of mate, a popular infused drink in parts of Latin America, may be related to increased cancer of the oral cavity though it is not known if the increased risk is due to its hot temperature, a potential carcinogenic effect of mate, or a combination of the two.[35,36] Fruits and vegetables are protective against OCPC; a pooled analysis indicated that high vegetable consumption was associated with a 50% reduction in OCPC.[37] In contrast, individuals with diets high in meat and dairy, controlling for alcohol and tobacco consumption, are at an increased risk of cancer of the oral cavity.[38] Other factors related to oral cavity cancer include a family history as cases with a first-degree relative with cancer of the oral cavity are at an increased risk for the disease after taking into account their consumption of alcohol and tobacco.[39] Inheritable disorders, including Fanconi anemia, are also linked to cancer of the oral cavity.[40] Additional genetic mutations that may be related to oral cavity mutation include germline mutations in p16.[41]

Descriptive Statistics

Incidence Patterns

Cancer of the oral cavity and pharynx is more common in males than females as shown in Tables 4.1 and 4.2.[42] The higher incidence among males compared to females is likely due to higher smoking rates and alcohol consumption among males. Incidence increases with age; incidence rates among those <40 years of age are <7 per 100,000 and increase to 11.7 among those aged 45 to 49. Incidence rates continue to increase to 19.9 per 100,000 for ages 50 to 54 and double by the age of 70 to 74 where the incidence rate is 40.1 per 100,000.[42] Globally, the age-standardized incidence rates for cancer of the oral cavity in developed and developing countries are estimated at 6.9 per 100,000 men and 4.6 per 100,000 men, respectively.[43] Cancer of the oral cavity and pharynx is nearly equivalent among women in developed (2.4 per 100,000 women) and developing (2.6 per 100,000 women) countries.[43] Among men in the United States, Whites have the highest age-adjusted incidence of cancer of the oral cavity and pharynx (16.7 cases per 100,000 men) followed by Blacks (14.9 per 100,000 men), Asian/Pacific Islanders (11 per 100,000 men), American Indian/Alaska Natives (11.1 cases per 100,000 men), and Hispanic men (9.3 per 100,000) (Fig. 4.2).[2] For females, the incidence of OCPC is also highest among whites; however, the differences by race are less marked than patterns observed for males (Fig. 4.3).[2] The overall higher incidence of cancer of the oral cavity and pharynx among whites compared to blacks reflects higher smoking rates among whites compared to blacks.[44] Furthermore, the prevalence of adult blacks who report any alcohol consumption and heavy alcohol consumption is less than that of whites.[45] Incidence patterns by race vary by subsite where the incidence of cancer of the palate, tonsil, and pharynx was higher among blacks than whites for males and females. Cancer of the lip is more common in whites than blacks; this difference may in part be due to higher susceptibility to solar keratosis among whites.[46]

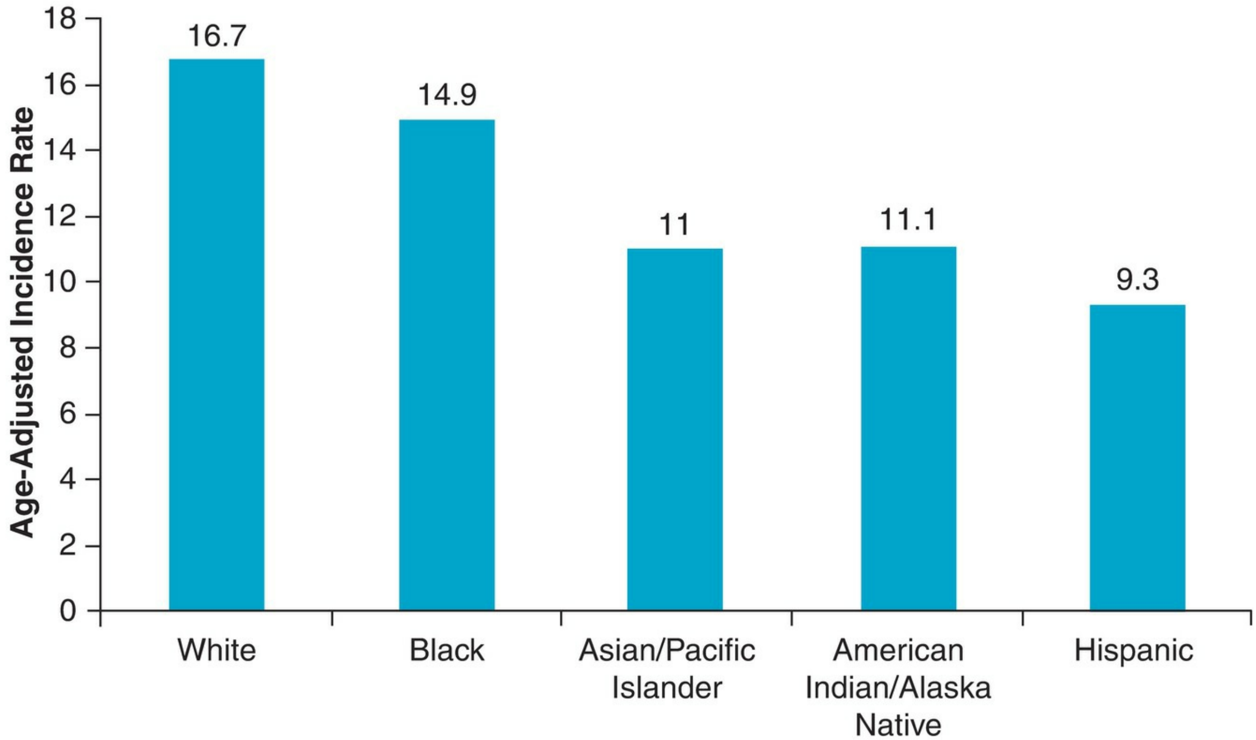

Figure 4.2. Age-adjusted incidence of cancer of the oral cavity and pharynx by race/ethnicity among males, SEER 18 2006–2010. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

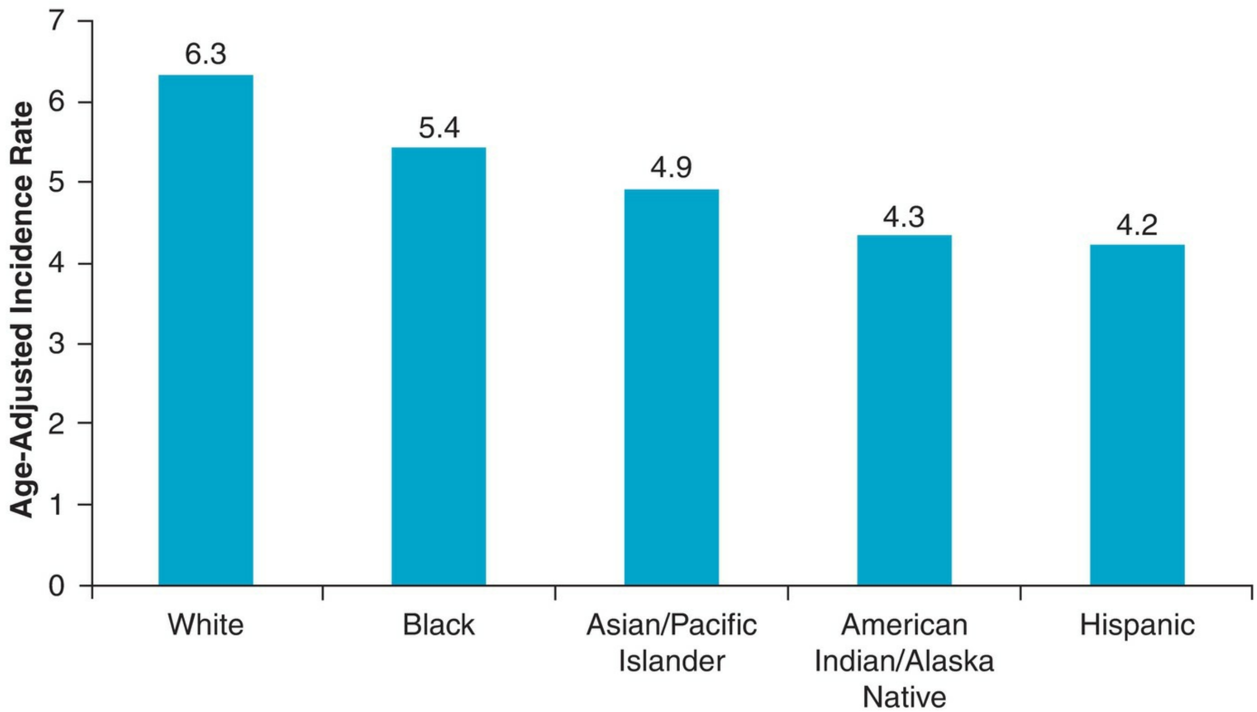

Figure 4.3. Age-adjusted incidence of cancer of the oral cavity and pharynx by race/ethnicity among females, SEER 18 2006–2010. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

Most recent studies of trends in cancer of the oral cavity and pharynx have been examined in the context of HPV-associated and non–HPV-associated cancers. HPV-associated cancers include lingual tonsil, palatine tonsil, and Waldeyer ring, whereas non–HPV-associated cancers include tongue, gum, floor of the mouth, and palate.[47] HPV-related squamous cell carcinoma (SCC) of the oral cavity and oropharynx have been increasing, whereas non–HPV-associated SCC of the oral cavity and oropharynx have been decreasing as depicted in Figure 4.4.[47–49] Between 1988 and 2004, HPV-related OPSCC increased 225% whereas HPV-unrelated OPSCC declined 50% during the same time period.[49] Starting in 2004, the incidence of HPV-related OPSCC and OCSCC approached non–HPV-related OPSCC and OCSCC.[47] Declines in HPV-unrelated OPSCC are attributed to the

reduced prevalence of cigarette smoking in the United States as well as decreases in per capita use of hard alcohol.[47] Smoking prevalence for adults in the United States has decreased from 42.4% in 1965 to 18.9% in 2011.[44] HPV-related OPSCC and OCSCC have increased across all age groups; however, there are particularly marked increases in more recent birth cohorts, suggesting differences in sexual practices over time. Though data on HPV prevalence in cancers of the oral cavity over time are limited, a study in Colorado reported that the prevalence of HPV in cancer of the oropharynx rose from 33% in the 1980s to 82% in the mid-2000s.[50]

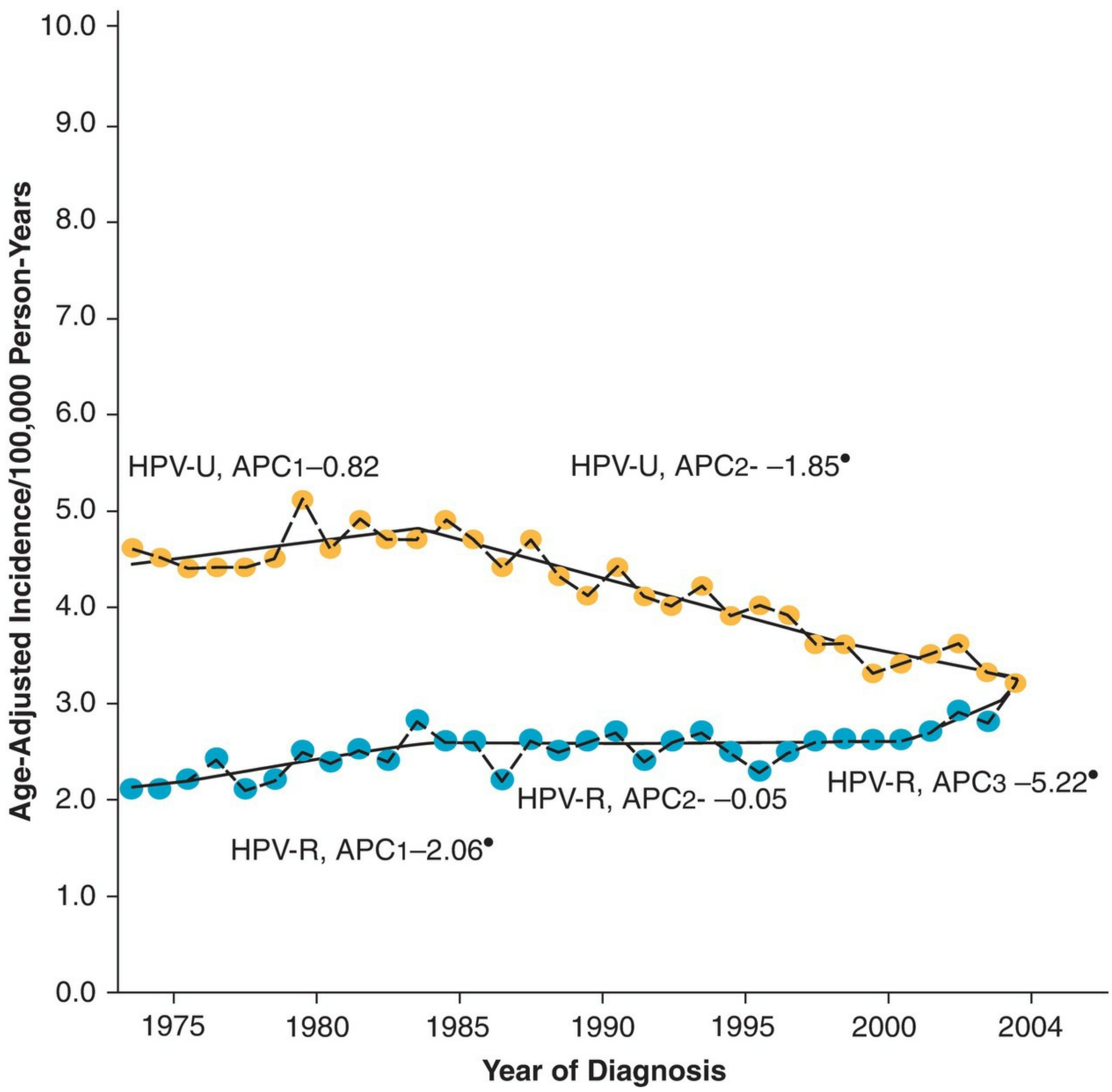

Figure 4.4. Incidence of HPV-related and HPV-unrelated squamous cell carcinomas of the oral cavity, 1975–2004. (Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol.* 2008;26:612–619.)

In general, HPV-related OPSCC and OCSCC incidence has increased among white men; however, the incidence among black males has declined.[51] This opposing temporal trend for black and white males has led to dwindling overall differences in black–white incidence rates as shown in Figure 4.5 where incidence trends for squamous cell carcinoma of the oral cavity and pharynx (excluding lip, salivary glands, and nasopharynx) are displayed. For example, the incidence of HPV-related OSCC for black men was double that compared to white men between 1973 and 1991, and between 1992 and 2007, the increased incidence among black men was only 43% higher.[51] A recent study also found that HPV-related OSCC incidence rates particularly increased for men residing in low socioeconomic neighborhoods.[52] For women, HPV-related OPSCC and OCSCC have recently declined for both black and white women, though the incidence among black women remains 25% higher relative to white women. Asian/Pacific Islanders and Hispanics have significantly lower HPV-related OCSCC and OPSCC compared to whites for both males and females.[51] These temporal differences in incidence by race may reflect differences in sexual practices by race/ethnicity.[51]

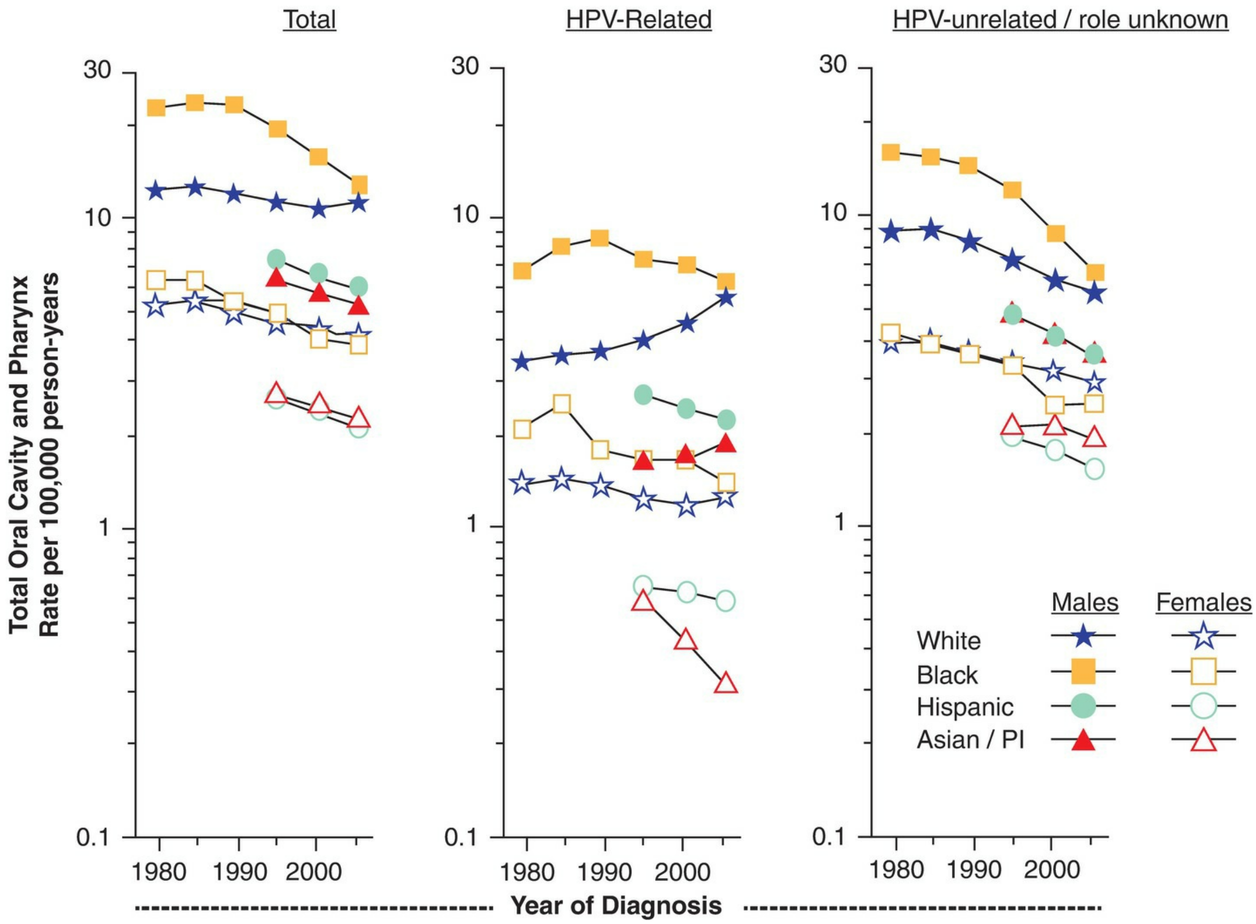

Figure 4.5. Age-adjusted HPV-related and HPV-unrelated squamous cell carcinoma of the oral cavity by diagnosis year, race, and gender, 1977–2007. (Brown LM, Check DP, Devesa SS. Oropharyngeal cancer incidence trends: diminishing racial disparities. *Cancer Causes Control.* 2011;22:753–763.)

Prognosis

Approximately one-third of cases of cancer of the oral cavity and pharynx are diagnosed with localized disease, 47% are diagnosed with regional disease, 17% are diagnosed with distant-stage disease, and 6% are unstaged. The prognosis for cancer of the oral cavity and pharynx is not favorable; the overall survival rate for cancer of the oral cavity and pharynx is 62% and ranges from 36.3% among distant stage to 82.7% for localized stage. Stage-specific survival rates have improved throughout time; between 1977 and 1991, the 5-year relative survival rate among localized cancers was 61.4% and increased to 72.9% between 1992 and 2006. During the same time intervals, the gains observed for regional- and distant-stage disease were even

more noticeable as survival increased from 36.8% to 52.5% among regional disease and 15% to 27.6% for distant-stage disease.[51] There has been some improvement in the 5-year survival of cancer of the oral cavity and pharynx across all race and gender categories since the mid-1970s as well (Fig. 4.6).[2] The 5-year relative survival rates among black males have increased the most with a 36% increase in survival from the mid-1970s to mid-2000s. During the same time period, white males experienced a 20% increase whereas white females and black females' 5-year relative survival increased by 17% and 11%, respectively.

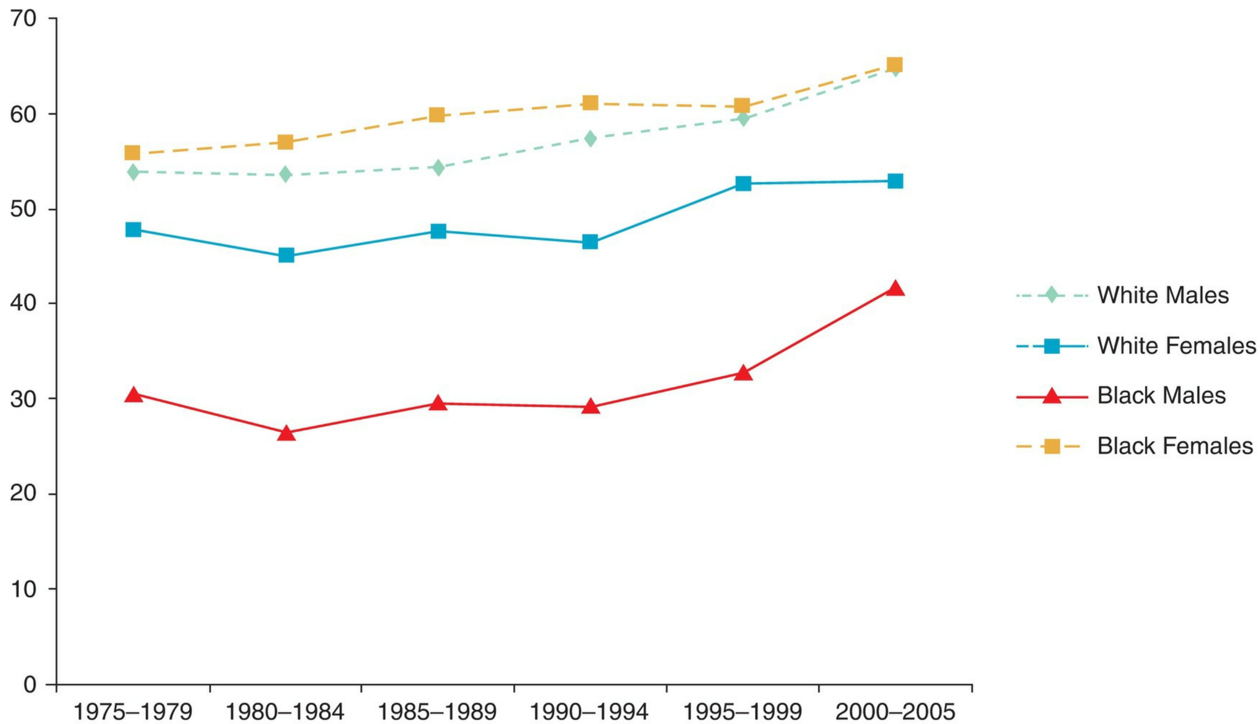

Figure 4.6. A 5-year relative survival for cancers of the oral cavity and pharynx by race and gender, SEER 18 1975–2005. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

Despite gains in survival over time, there remains a considerable survival disparity by race. Recent 5-year relative survival rates are 63.6% for white

males and 38.6% for black males, whereas the 5-year relative survival for white and black women is 64.6% and 53.0%, respectively. Some of these survival disparities are attributed to later stage at diagnosis.[53,54] Figure 4.7 demonstrates that blacks are disproportionately diagnosed at advanced stage, which may be attributed to delays in diagnosis and access to care. One study examining cancer of the oropharynx did not observe increased advanced-stage disease among blacks when insurance was adjusted for, which supports the hypothesis that access to care is one component of advanced-stage disease among blacks.[55] However, blacks have poorer survival even among those with localized cancer, indicating that other factors, including lower socioeconomic status (SES) and suboptimal treatment, also contribute to poorer survival among blacks than whites.[53] Black patients with cancer of the oral cavity and pharynx were less likely to receive cancer-directed surgery and more likely to receive radiation without chemotherapy.[56] Even after adjusting for treatment, insurance, and other sociodemographic factors, blacks had a 45% increased risk of all-cause death in a recent study of over 20,000 cases of cancer of the oropharynx.[57] Some of the increased hazard of death among blacks could be due to other competing causes of death as this study examined overall survival; however, after adjusting for comorbidity, blacks still had a higher hazard of death in this study.

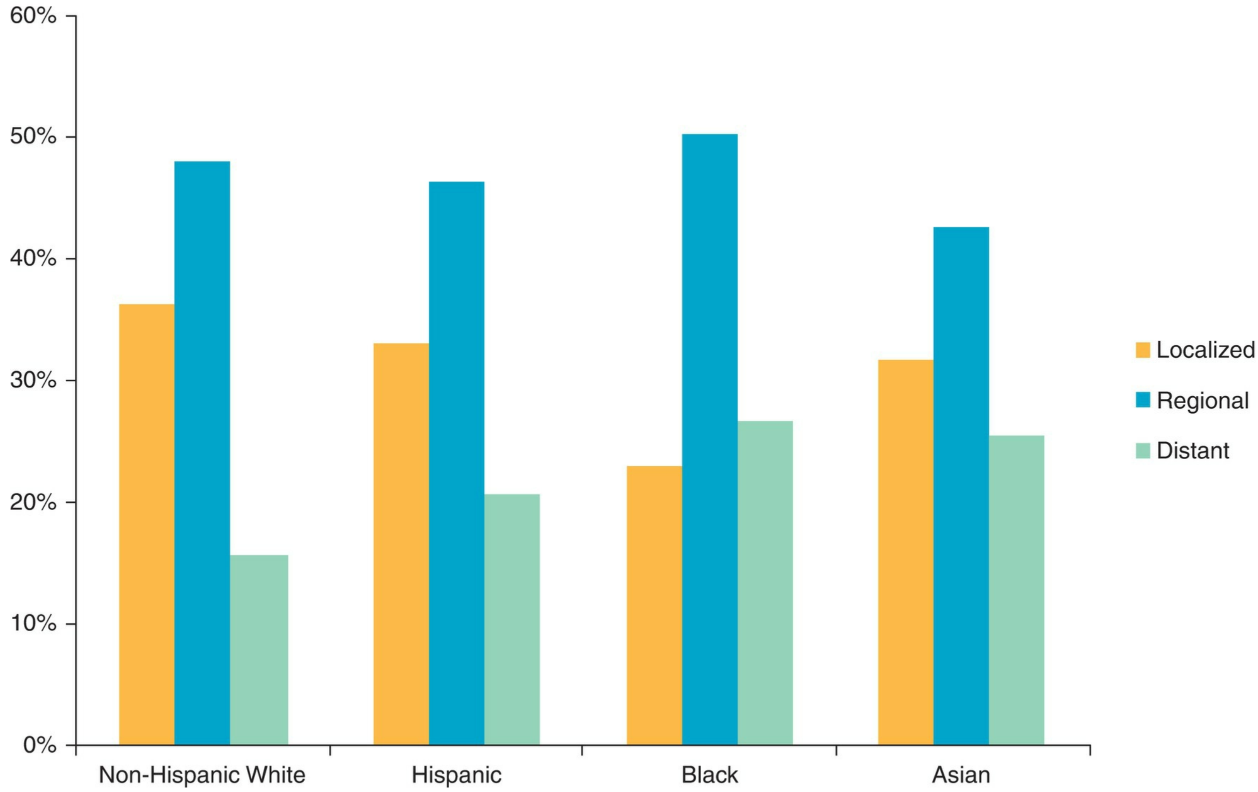

Figure 4.7. Stage distribution among cancers of the oral cavity and pharynx by race/ethnicity, SEER 18 2000–2010. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

Interestingly, the proportion of Asian Americans diagnosed at late stage (26%) is similar to that of Blacks (27%). Despite this similarity, the 5-year relative survival among Asian Americans is higher than that of any other race/ethnicity overall (Table 4.3). Among cases with distant stage, Asian Americans' survival is considerably higher than that of other race/ethnicities where survival among Asian Americans is ~50% compared to <40% among non-Hispanic Whites. Adjusting for stage in addition to other sociodemographic and clinical factors, the survival benefit among Asian Americans with cancer of the oropharynx, nasopharynx, and hypopharynx compared to Whites was not statistically significant.[58] However, similar factors including receipt of treatment, SES, and age were important predictors

of survival among Asians, which is what is observed for other race/ethnicities.[58]

Table 4.3 Five-Year Relative Survival for Pharynx Cancers of the Oral Cavity by Race/Ethnicity, Stage, and Gender, SEER 18 2003–2009

	Males				Females			
	Total	Localized	Regional	Distant	Total	Localized	Regional	Distant
Non-Hispanic White	63.7%	81.5%	63.4%	37.9%	64.8%	83.4%	56.1%	35.6%
Hispanic	57.0%	81.9%	56.9%	34.0%	69.1%	90.0%	58.6%	44.5%
Black	38.7%	72.6%	38.0%	23.2%	51.3%	82.3%	40.5%	29.1%
Asian	64.8%	86.4%	62.8%	50.6%	71.5%	85.3%	70.4%	50.8%

Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov

Studies have shown that HPV-positive patients with squamous cell carcinomas of the head and neck have better survival than do patients who are HPV negative.[59] In addition, significant reductions (59% to 83%) in cause-specific hazards of death for HPV-positive head and neck squamous cell carcinoma (HNSCC) have been reported, after adjusting for important confounders including age, clinical characteristics, and tobacco and alcohol consumption.[31,60] A meta-analysis reported a 15% reduction in overall hazard of death as well as marked disease-free survival among HPV-positive versus HPV-negative patients with cancer of the head and neck.[59] Although some of the aforementioned factors, including younger age at diagnosis, may explain some of the survival advantage among HPV-related OSCC tumors, it does not explain it entirely as several studies have adjusted for age and other prognostic factors. Improved survival among patients with squamous cell carcinoma of the oropharynx is likely multifactorial and is in part due to increased sensitivity of the cancers to radiation and response to chemoradiation.[61]

CANCER OF THE SALIVARY GLANDS

Cancer of the salivary glands is often included with cancers of the oral cavity and pharynx for etiologic and descriptive epidemiologic studies. Cancer of the salivary glands includes major salivary glands, including parotid, sublingual, and submandibular, as well as minor salivary glands found in the mucosa of the upper aerodigestive tract.

Cancer of the Major Salivary Glands

Cancer of the major salivary glands is uncommon, representing only 11% of the 41,380 cancers of the oral cavity and pharynx diagnosed each year; however, unlike other cancers of the oral cavity and pharynx that are almost all squamous cell cancer, the histology of cancer of the salivary glands is heterogeneous.[62] The incidence of cancer of the major salivary glands varies by histologic type; the most common histologic type is mucoepidermoid carcinoma (2.85 per 100,000), followed by squamous cell carcinoma (1.83 per 100,000), acinic cell carcinoma (1.38 per 100,000), adenoid cystic carcinoma (1.30 per 100,000), and adenocarcinoma NOS (1.22 per 100,000).[62] The remaining histologic types, which include salivary duct carcinoma, basal cell carcinoma, oncocytic carcinoma, clear cell adenocarcinoma NOS, cystadenocarcinoma, mucinous adenocarcinoma, polymorphous low-grade adenocarcinoma, sebaceous carcinoma, malignant mixed tumors, and other rare carcinomas, have incidence rates that are <1 per 100,000.[62] The most common site of cancer of the major salivary glands is the parotid gland (80%) followed by the submandibular (15%) and sublingual glands (4%).

Though major salivary glands have been included in some case–control studies as part of investigations of etiologic factors related to cancer of the oral cavity and pharynx, few studies have examined the etiologic factors specific to major salivary glands. In a case–control study with 150 cases of cancer of the major salivary glands and 191 controls, current smoking was associated with salivary gland risk among males. However, this study did not observe an association between smoking among women.[63] Additionally, two other case–control studies did not observe an association between smoking for men or women.[64,65] The association between alcohol consumption and salivary gland cancer occurrence is also unclear as some studies have reported a positive association among males,[63] whereas another reports a significant association for females only[64] and another study reported null

findings for both males and females.[65] Studies have more consistently reported an association between radiation exposure and cancer of the major salivary glands.[63,64,66] Some studies have reported an association between occupational exposures and cancer of the major salivary glands,[63,66] whereas others have not.[65]

The age-adjusted incidence rate of cancer of the major salivary glands is ~1.62 per 100,000 among males and 1.01 per 100,000 among females as shown in Table 4.4.[2] The incidence of cancer of the major salivary glands varies by age, sex, and histology. Among mucoepidermoid salivary gland cancers as well as all WHO-classified cancers combined, women have a slightly higher incidence compared to men until the fifth decade of life, and after that, the incidence of cancer of the major salivary glands is higher among males.[62] This age–gender interaction has not been explained though it is hypothesized that a hormonal component may be related to these findings.[62] A study of reproductive and hormonal factors related to major salivary glands did find a positive association between early menarche and null parity and cancer of the salivary glands, which is congruent with the hypothesis that hormones may be involved with salivary gland tumorgenesis.[67] However, the incidence of squamous cell carcinoma and non–WHO-classified tumors for men is markedly higher than that for females across all ages, which may indicate more distinct risk factors by histologic type.[62]

Table 4.4 Age-Adjusted Incidence of Cancer of the Major Salivary Glands by Sex, Site and Race/Ethnicity, and Age per 100,000 Person-Years, SEER 18 1990–2009

	Males	Females
Primary site		
Parotid gland	1.32	0.77
Submandibular gland	0.22	0.17
Sublingual gland	0.01	0.02
Overlapping lesion	<0.01	<0.01
Major salivary gland, NOS	0.06	0.05
Age		
<50 y	0.39	0.45
50–69 y	2.97	1.89
≥70 y	8.61	3.58
Race		
White	1.69	1.01
Black	1.27	0.94
Other	1.09	0.86

Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov

As shown in Table 4.4, the incidence of cancer of the major salivary glands among white males is slightly higher (1.69 per 100,000) compared to black (1.27 per 100,000) and men of other races (1.09 per 100,000). For females, there is little difference in age-adjusted incidence rates where the incidences for white, black, and other females are 1.01, 0.94, and 0.86 per 100,000, respectively. A study examining incidence patterns by histology and

race noted significantly lower incidence rates among blacks compared to whites for squamous cell carcinoma, and acinic cell carcinoma, but not for other histologic types.[62] The same study reported lower incidence rates of squamous cell, acinic cell, adenocarcinoma NOS, and non–WHO-classified tumors for Asian/Pacific Islanders compared to Whites.[62]

Approximately half of all cases of cancer of the major salivary glands are diagnosed with localized cancer (49.6%), 27.5% are diagnosed with regional metastases, and the remaining 12.9% are diagnosed with late-stage cancer.[2] The stage distribution varies by gender as the proportion of women diagnosed with localized disease (55%) is greater than that of men (39%) and men have a higher proportion of regional (39%) and distant stage (14%) compared to women (29% regional, 9% distant).[2] Black men (46%) and men of other races (50%) are more likely to be diagnosed with early-stage cancer compared to whites (41%), though the proportion of distant-stage cancer is generally the same across racial groups (14% to 16%).[2] Among females, the stage distribution is essentially the same across racial groups. The stage distribution does vary with histologic type. For major salivary glands, mucoepidermoid, adenocarcinomas, and adenoid cystic carcinomas tend to be diagnosed at earlier stages as 59.7%, 54.2%, and 49.6%, respectively, are diagnosed with localized cancer, whereas only 23.4% of squamous cell and 18.7% of non-WHO are diagnosed with localized cancer.[2]

The estimated 5-year relative specific survival rate for males is 67.2%. Females have a better prognosis with 5-year relative survival of 80.5%,[68] which is likely due to women's more favorable stage distribution. Survival decreases steeply with age. The 5-year survival rate for cases diagnosed before the age of 50 is ~90%, whereas the 5-year relative survival rate declines to 75% among cases diagnosed between the ages of 50 and 64.[68] Further declines in survival are observed for cases aged 65 to 74 (68%) and cases 75 years and older (55%). Unlike other cancers of the oral cavity and pharynx, survival is similar across racial groups.

However, histologic type does impact survival. Among cancers of the parotid gland, 5-year survival for acinic cell carcinoma and mucoepidermoid carcinoma had the highest rates, which were both ~80%. Furthermore, high-grade mucoepidermoid cancer had significantly worse survival than did low or intermediate grade (40% vs. 80%). In fact, tumor grade within each

histology was an independent prognostic factor. The 5-year survival rates among adenocarcinomas (66%), malignant mixed tumor (73.3%), adenoid cystic carcinoma (70.1%), and squamous cell carcinomas were lower (46.1%).[69] Other factors related to survival include the presence of positive nodes, extraglandular extension, and cancer grade; a multivariate analysis demonstrated that these pathologic features and age were the most important predictors of survival.[69]

Cancer of the Minor Salivary Glands

Cancer of the minor salivary glands is rare, which is reflected in the paucity of data on these cancers. Cancer of the minor salivary glands may arise from the 500 to 1,000 salivary glands located throughout the mucosa of the upper aerodigestive tract.[70] The most common sites for cancer of the minor salivary glands to occur is the hard palate, upper lip, base of the tongue, and buccal mucosa.[70] The most common histology is mucoepidermoid carcinoma (49.8%), followed by adenoid cystic carcinoma (26.3%), adenocarcinoma (21.7%), and acinic cell carcinoma (2.2%) according to data from 639 minor salivary gland carcinomas in the SEER database.[71] The causes of cancer of minor salivary gland origin are largely unknown, and the risk factors for cancer of the minor salivary glands are often not delineated from those cancers of the major salivary glands.

Some studies have reported a higher proportion of females compared to males,[70] and according to population-based SEER data on 639 cases, 45% of cases were male and 55% were female.[71] According to this study based on SEER data, the majority of cancers of minor salivary gland origin do present with nodal involvement and 43%, 19.4%, 2.8%, and 35.2% are diagnosed with T1, T2, T3, and T4 stage, respectively.[71] Several single-institution studies have reported survival rates ranging from 66% to 80% 5 years after diagnosis and 57% to 70% 10 years after diagnosis.[70,72–76] According to SEER data, the median survival time is ~13.15 years, which is generally consistent across histologic types.[71]

CANCER OF THE LARYNX

Cancer of the larynx is the 21st most frequently occurring cancer among

males and females in the United States.[77] In 2012, an estimated 12,260 patients will be diagnosed with cancer of the larynx and 3,360 will die from the disease in the United States.[77] Approximately one-half of cancers of the larynx arise in the glottis (52%), and one-third arise in the supraglottis (34%), and over 95% of cancers of the larynx originate from squamous cells.[2] The median age at diagnosis is 65 years of age and the median age at death is 68 years.[42]

Risk Factors

Tobacco and alcohol are the primary risk factors for cancer of the larynx. The population attributable risk for tobacco is greater (52%) than that for alcohol (3%).[78] In 1986, the IARC confirmed tobacco as a cause for cancer of the larynx.[79] The risk associated with smoking varies widely; some reports have noted odds ratios around 4, whereas others have reported odds ratios over 20.[7,80] A pooled analysis of case–control studies found odds of cancer of the larynx that were 6.8 times higher in tobacco users compared to nontobacco users among nondrinkers.[78] Tobacco appears to have a stronger effect on cancer of the supraglottis compared to cancer of the glottis.[80,81] There is also a dose–response relationship between tobacco and cancer of the larynx; as the number of cigarettes smoked per day and the number of pack years smoked increases, so do the odds of laryngeal cancer.[7,78,82] Former smokers have lower odds of laryngeal cancer compared to current smokers.[80] Cessation of smoking is thought to lower the risk of cancer of the larynx in case–control studies[80,81]; however, a pooled analysis showed no statistically significant reduction of cancer of the larynx after cessation of smoking.[83] In addition to cigarette smokers, cigar and pipe smokers are at an increased risk of laryngeal cancer.[7] Conversely, studies of Indian men showed no association between chewing tobacco and laryngeal cancer[84] and studies of Swedish men noted a null association between snuff use and cancer of the larynx.[15]

In 2007, IARC concluded that alcohol was a risk factor for laryngeal cancer.[85] The evidence for low consumption of alcohol intake and cancer of the larynx is less clear and weaker than the observed associations between moderate and heavy alcohol intake and cancer of the larynx.[86,87] In this meta-analysis, light drinking (≤1 drink per day) was not associated with cancer of the larynx, but moderate (>1 and <4 drinks per day) and heavy drinking (≥4

drinks per day) were associated with a 1.5 and 2.5 increased odds of cancer of the larynx, respectively.[87] Most studies examining cancer of the larynx and alcohol have been of case–control design. One cohort study found no association between alcohol and cancer of the larynx[88] whereas another observed an increasing risk of cancer of the larynx among women consuming >7 drinks per week.[86] Additionally, a pooled analysis observed an association between cancer of the larynx and heavy consumption of alcohol.[78] The variation in the magnitude and significance of the effect of alcohol on cancer of the larynx could be due to a variety of factors including unmeasured confounding and exposure misclassification because the use of alcohol is frequently underreported, particularly among those who are heavy drinkers.

Tobacco and alcohol are synergistically related to cancer of the larynx, meaning the risk of cancer of the larynx among those who smoke and drink is greater than the independent effects of each.[7,80,81,89] A pooled case–control study reported nonsmokers who consumed 29 to 35 drinks per week had OR of 1.6, which increased to 5.0 for light smokers, 7.1 for intermediate smokers, and 10.4 for heavy smokers.[7] In contrast to other reports observing an interaction,[7,80,89] a pooled analysis of case–control studies found increasing odds ratios associated with both smoking and drinking, but the statistical test for interaction was not significant.[78] The interaction between these two exposures is not fully understood, and untangling the effects of alcohol from tobacco is difficult as many heavy drinkers are also smokers.[80] Furthermore, there is still some debate over the role of a biologic interaction versus a statistical interaction.[80]

The relationship between gastroesophageal reflux disease (GERD) and cancer of the esophagus has been established, which has led researchers to examine the association between GERD and cancer of the larynx, which is in close proximity to the esophagus. Among nonsmokers and nondrinkers, the odds of cancer of the larynx were 1.78 among those reporting heartburn compared to individuals with no reported heartburn.[90] A meta-analysis of four studies found a pooled odds ratio of over 2 for GERD and laryngeal cancer[91]; however, results were heterogeneous and a subsequent case–control study reported no association.[92]

The role of HPV on laryngeal squamous cell carcinoma is not as clear as for cancer of the oropharynx. The prevalence of HPV in cancer of the larynx

from tissue across 55 studies ranged from 0% to 79% with an average of 28%.[93] Case–control studies examining this issue have reported varied results and varied methods of HPV detection. A systematic review of six studies reported a pooled odds ratio of cancer of the larynx among HPV-positive cases to be 2.5 (95% CI 1.4 to 4.4)[94] indicating an association between squamous cell carcinoma of the larynx and HPV; however, an aforementioned case series study reported a low proportion of HPV-positive cases of cancer of the larynx. Therefore, the results are mixed and not strongly indicative of an association between HPV and cancer of the larynx.

There are several other risk factors for cancer of the larynx. Dietary risk factors have been associated with cancer of the larynx. Consumption of animal products[95] has been shown to be associated with cancer of the larynx, whereas consumption of fruits and vegetables is inversely associated with cancer of the larynx.[82,96] There are several occupational exposures that have been proposed as risk factors for cancer of the larynx with varying degrees of certainty, and the number of cases of cancer of the larynx related to occupational exposures is estimated to be <3%.[97] Several occupational exposures including asbestos, wood dust, cement, and coal dust have also been suggested as potential risk factors for cancer of the larynx.[98–100] However, a systematic review of asbestos found no association between cancer of the larynx and asbestos,[101] and another study only found a weak association.[102]

Descriptive Epidemiology

Incidence

The incidence of cancer of the larynx is higher in males compared to females. Incidence also increases with age where the incidence rate among individuals <50 years of age is <8 per 100,000. The incidence for those aged 45 to 54, 55 to 64, and 65 to 74 is 16.2, 30.2, and 28.6 per 100,000, respectively. At about the age of 75, the incidence of cancer of the larynx begins to decline more significantly where the incidence drops to 17.0 per 100,000 and declines to 4.8 per 100,000 among those aged 85 years and older.[42]

The incidence of cancer of the larynx is higher for men in developed (5.5 per 100,000 men) compared to developing countries (3.5 per 100,000 men).[43]

Within the United States, the age-adjusted incidence rate of cancer of the larynx is highest among black men (9.6 cases per 100,000 men), ~1.6 times higher than whites. The incidence rate for Hispanics is similar to that of Whites, and incidence rates for Asian/Pacific Islanders is slightly lower (see Table 4.1).[2] For females, the incidence of cancer of the larynx is similar between developing and developed countries with age-standardized incidence rates of 0.6 per 100,000 women. Within the United States, the incidence of cancer of the larynx is low among women (1.12 cases per 100,000 women) and rates are generally similar across race/ethnicities although there is a slightly elevated incidence of cancer of the larynx among black women (IR compared to whites 1.47, 95% CI 1.28 to 1.66) (see Table 4.2).[2] The higher incidence of cancer of the larynx among black males is not fully explained by smoking and alcohol consumption as blacks have slightly lower smoking rates and are less likely to drink heavily than are whites.[44,45] Blacks also have a higher incidence[42] of cancer of the lung and at least one study examining black–white differences in cancer of the lung risks suggests that blacks may smoke more intensely (i.e., smoke more cigarettes per day) than do whites, which may partially explain higher incidence rates of cancer of the larynx among blacks despite lower smoking prevalence.[103]

Cancer of the larynx also varies by geographic location. For males, cancer of the larynx is high in the southeastern states, sometimes referred to as the "tobacco belt." A similar geographic pattern is not evident for women.[104] The male incidence patterns reflect higher smoking prevalence among southeastern states, which range from 21% to 29% compared to <20% for states located outside this area.[105] Studies examining incidence of cancer of the larynx by education have not been conducted, as individual-level education status is not available in population-based registries. However, smoking prevalence is highest among non–high school graduates; about 47% of adult males with a high school education smoke compared to <10% for college graduates.[105] Similar patterns are observed for women.[105]

Statistically significant declines in the incidence of cancer of the larynx in the United States have been largely attributed to reductions in smoking rates, and in the most recent time period, cancer of the larynx has decreased by 2.6% and 2.3% per year for males and females, respectively (Fig. 4.8). The declines in the incidence of cancer of the larynx for men began before the decline for women, which is due to temporal trends in smoking rates.

Male smoking prevalence peaked in the 1950s and 1960s, and female smoking prevalence did not peak until the late 1960s.[106] Current smoking rates have been stabilized at around 21.6% and 16.5% for men and women, respectively.[44] Alcohol consumption patterns have also declined in the United States since 1980, which may partially explain declines in the incidence of cancer of the larynx.[107]

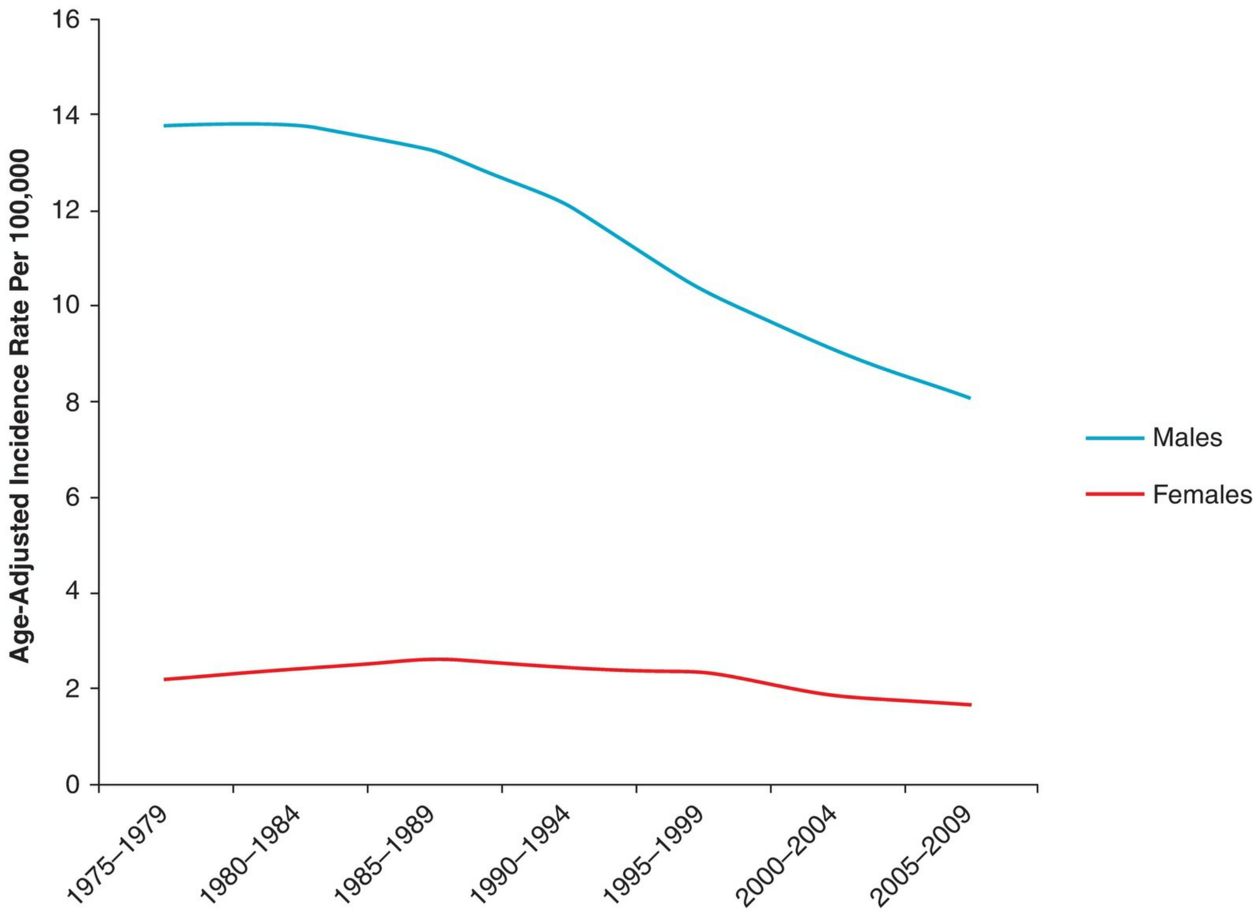

Figure 4.8. Age-adjusted incidence rates for cancer of the larynx by diagnosis year, and sex, SEER 18 1975–2009. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

Prognosis

Approximately 60% of cancers of the larynx are diagnosed with localized cancer, 21% are diagnosed with regional metastases, and 19% are diagnosed with distant metastases. Stage at diagnosis varies by race/ethnicity as 52% of black men are diagnosed with localized cancer compared to 64%, 63%, and 60% among non-Hispanic Whites, Asians, and Hispanics (Fig. 4.9). Over half (56%) of non-Hispanic White and Hispanic women are diagnosed with localized cancer compared to only 42% of black women (Fig. 4.10). Though the proportion of Asian women diagnosed with localized disease is slightly lower (48%) than that of non-Hispanic White and Hispanic women, they have the lowest proportion of distant-stage cancer (15%). Black–white differences in stage at diagnosis have been noted among National Cancer Data Base (NCDB) patients after adjusting for other factors.[108] Some of these differences may be related to access to care; yet, the aforementioned NCDB study reported a 38% increase in odds of advanced laryngeal cancer for blacks compared to whites after adjusting for insurance status as well as other sociodemographic factors.[108] This finding suggests that other factors may contribute to delays in seeking care including cultural or social barriers. It is worth noting that insurance seems to be a stronger predictor of advanced stage as Medicaid and uninsured patients were two times as likely to be diagnosed with advanced-stage cancer of the larynx compared to privately insured patients after adjusting for other factors.[108] Uninsured and Medicaid-insured patients are less likely to have a usual source of care and may delay seeking care for symptoms of cancer of the larynx that include hoarseness, dysphagia, and voice changes.[108]

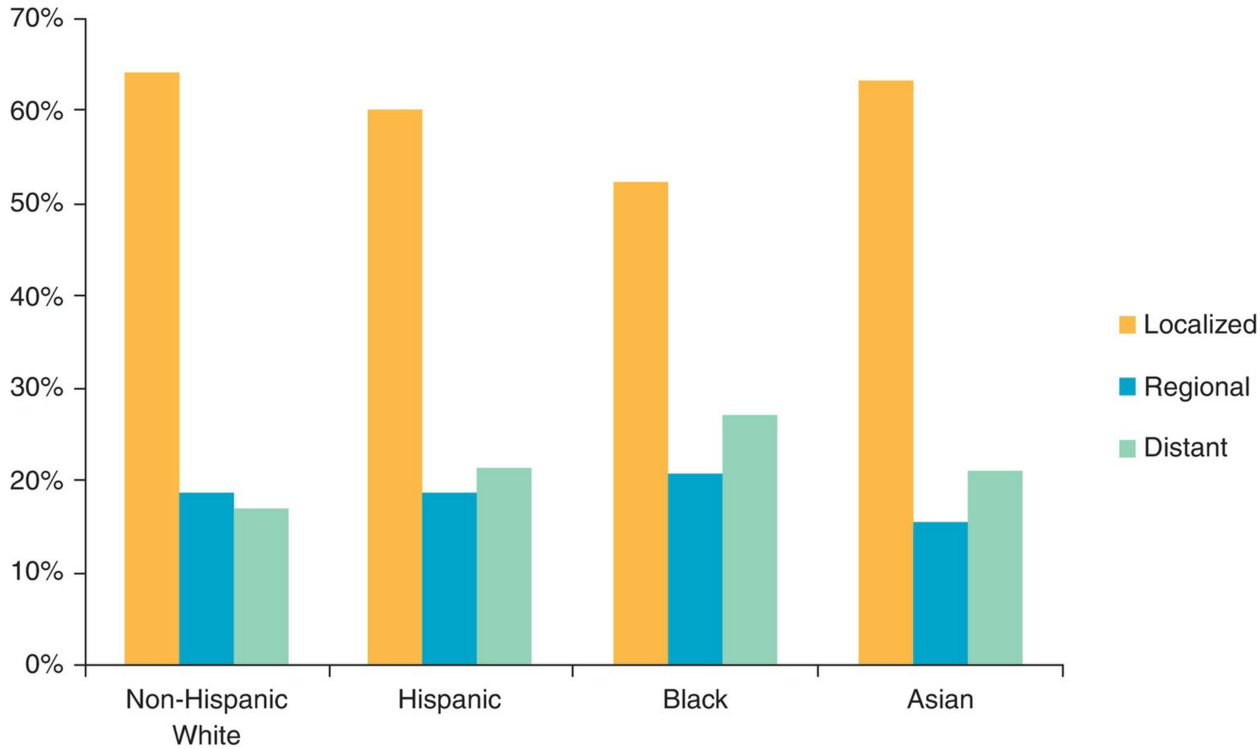

Figure 4.9. Stage at diagnosis for cancer of the larynx by race/ethnicity among males, SEER 18 2000–2009. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

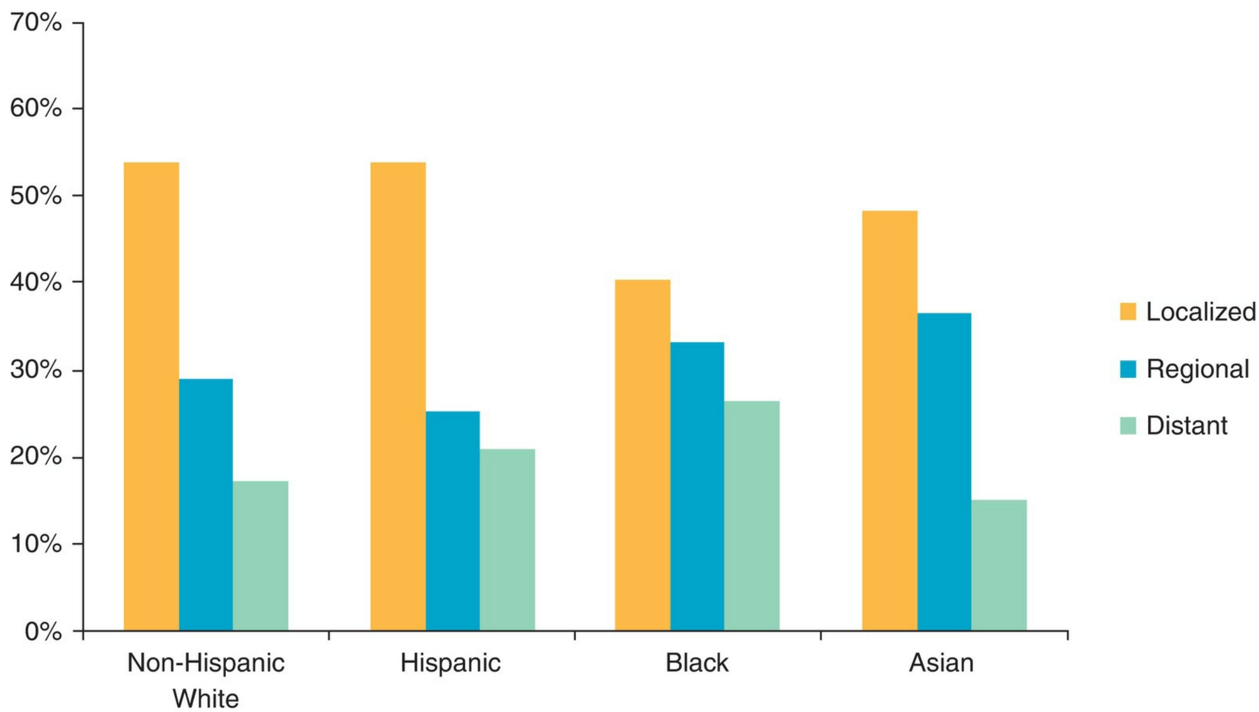

Figure 4.10. Stage at diagnosis for cancer of the larynx by race/ethnicity among females, SEER 18 2000–2009. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

Black men have a poorer 5-year relative survival (55.2%) compared to white men (62.4%) (Table 4.5). The survival disparities are likely multifactorial as a study adjusting for stage and other sociodemographic factors noted a statistically significant higher hazard of death among blacks compared to whites.[109] The 5-year relative survival for Hispanic men is slightly lower compared to non-Hispanic White males, whereas Hispanic females have slightly higher survival than do non-Hispanic White females (Table 4.5). However, these survival differences by Hispanic ethnicity are not observed in studies adjusting for clinical, demographic, and treatment-related factors.[109] Asians have a slightly better 5-year relative survival compared to non-Hispanic Whites among males and females.

Table 4.5 Five-Year Relative Survival for Cancer of the Larynx by Gender and Race/Ethnicity, SEER 18 2004–2009

	Males				Females			
	Total	Localized	Regional	Distant	Total	Localized	Regional	Distant
Non-Hispanic White	66.0%	77.1%	42.7%	34.9%	60.7%	69.7%	43.0%	37.8%
Hispanic	61.2%	69.4%	42.3%	39.4%	65.1%	71.5%	a	40.0%
Black	54.2%	75.0%	40.5%	33.8%	51.1%	69.4%	39.4%	40.9%
Asian	68.2%	83.5%	44.7%	36.0%	64.2%	89.0%	57.0%	*

Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov

[a]Statistic could not be calculated due to sparse data.

Mortality from cancer of the larynx has declined from 1.69 per 100,000 individuals to 1.08 per 100,000 in 2009 in the United States.[42] These declines are due to changes in incidence, as the survival rate for cancer of the larynx has not improved over time.[42,110,111] In fact, some studies have suggested decreases in survival for cancer of the larynx, particularly for advanced stages.[110–112] Cosetti et al.[110] suggest several explanations for the decline in survival, including spurious associations in earlier time periods and better survival of competing risks leading to more patients with cancer of the larynx dying from cancer as opposed to other causes. Stage drift (i.e., more localized cancers being considered as later stages) and detection of cancers earlier do not contribute to the observed declining survival over time as inclusion of less advanced cancers would actually improve survival statistics among late-stage disease.[110] One study found declining survival only among middle-aged patients and suggested a birth cohort effect as potential reason for declining survival among patients with cancer of the larynx.[110] Another reason suggested for declines in survival is related to changes in treatment protocols for cancer of the larynx.[110,111] In 1991, the Veterans Affairs Laryngeal Cancer Group demonstrated equivalent survival among advanced-stage patients treated with chemoradiation as compared to advanced-stage patients treated with laryngectomy, which was the primary form of therapy before the trial.[113] Since this trial, laryngectomies among advanced-stage patients have

declined from over 50% in the late 1980s to around 30% in 2007 with a concomitant increase in chemoradiation from <10% in the 1980s to around 50% by 2007.[109]

CANCER OF THE THYROID

There are several distinct histopathologic subgroups of cancer of the thyroid. Approximately 90% of cancers of the thyroid arise from the epithelial tissue and are well-differentiated papillary and follicular carcinomas (PFCs). PFC have a good prognosis with 5- and 10-year cause-specific survival rates of 98% to 96%, respectively.[2] Anaplastic cancers, which also arise from the epithelial tissue, only represent 1% to 2% of cases diagnosed but are highly fatal with a survival rate of <10% within 5 years of diagnosis.[2,114,115] Only 5% to 10% of cases are diagnosed with medullary thyroid carcinomas (MTCs) with a survival rate that is estimated to be 86% and 65% after 5 and 10 years after diagnosis, respectively (Table 4.6).[116,117]

Table 4.6 Five-Year Relative Survival for Carcinoma of the Thyroid by Race/Ethnicity and Histologic Type, SEER 18 2000–2005

	Anaplastic	Medullary	Follicular	Papillary
Non-Hispanic White	8.8%	86.0%	95.7%	99.2%
Hispanic	6.9%	81.6%	95.0%	98.1%
Black	9.3%	78.4%	92.2%	98.0%
Asian	9.9%	87.7%	94.0%	97.9%

Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov

Risk Factors

It is estimated that 25% of medullary thyroid cancers are hereditary and are a result of three syndromes: multiple endocrine neoplasia (MEN) type 2A, MEN type 2B, and familial medullary thyroid carcinoma.[118] The remaining sporadic MTC are largely unexplained. A pooled analysis of case–control studies across Europe, North America, and Asia aimed at understanding risk factors for sporadic MTC reported positive associations between MTC and benign thyroid disorders, gall bladder disease, and hypertension, though these factors have not been widely studied.[119]

The causes and risk factors for anaplastic cancers are not well understood, though studies have associated elevated risk with prior history of goiters and several genetic alterations, including alterations of p53.[120] Genetic factors, specifically rearrangement of the oncogene RTEN and BRAF mutations, are associated with papillary thyroid cancer.[121] There are several other reported risk factors for papillary and follicular cancers including age, gender, and radiation. The relationship between cancer of the thyroid and radiation exposure was established following the study of survivors of the atomic bombs in Hiroshima and Nagasaki in the 1940s.[122,123] The strong association between radiation and cancer of the thyroid was further studied and confirmed with the study of individuals exposed to the 1986 Chernobyl Disaster.[124,125] Exposure to radiation during childhood has been shown to be particularly important as risk ratios for cancer of the thyroid among children exposed to high doses of radiation notably exceeds that of adults exposed to similarly high doses of radiation.[124] These findings highlight the sensitivity of naive thyroid tissue to radiation exposure. Prior treatment of childhood cancer is also associated with an increased risk of cancer of the thyroid.[126] However, the risk of low-dose radiation in childhood, which is much more prevalent in the general population, on cancer of the thyroid is unclear as it is difficult to ascertain low-dose exposure levels. Additionally, models extrapolating risks of high-dose exposures to low-dose exposures may not be accurate, though it may be reasonable to assume a linear dose–response for some forms of radiation.[127]

Unlike other cancers of the head and neck, tobacco exposure is not positively associated with cancer of the thyroid. In fact, there is a growing body of research suggesting an inverse association between papillary and

follicular thyroid cancer and tobacco exposure.[128–130] A pooled analysis of prospective studies reported current smokers had a statistically significant 30% decreased risk of cancer of the thyroid compared to never smokers,[129] and there was no significant association noted for former smokers. However, some studies have shown decreased risk in never smokers.[130] Additionally, dose–response relationships have been noted with declines in risk of cancer of the thyroid with increasing duration and amount of cigarette use.[130] The mechanism through which smoking decreases thyroid cancer risk is thought to be through decreased thyroid stimulation hormone among smokers.

The association between other thyroid disorders and cancer of the thyroid has mixed results and is difficult to examine given the increased probability of detecting indolent cancer of the thyroid in populations seeking medical treatment for these disorders that include goiters, hypothyroidism, and hyperthyroidism.[131] The relationship between cancer of the thyroid and Hashimoto thyroiditis,[132] an autoimmune disease responsible for hypothyroidism, is unclear. A systematic review of the literature did not support an association between cancer of the thyroid and Hashimoto thyroiditis among population-based studies with fine needle aspiration–biopsied cancers, but an association was noted for studies examining thyroidectomy specimens, which are subject to selection bias.[133] A pooled analysis reported a null association between hypothyroidism and thyroid cancer and only a tentative association between hyperthyroidism and thyroid cancer.[134] This pooled analysis,[134] however, reported a higher risk of cancer of the thyroid among those with a history of a goiter as well as those with a history of a benign disorder of the thyroid.

Other suggested risk factors for cancer of the thyroid include dietary factors. One study reported that iodine deficiency is related to follicular carcinoma risk whereas excess iodine intake is related to papillary carcinoma[135]; however, other studies reveal inconsistent findings.[136] Ecologic studies comparing the incidence of cancer of the thyroid before and after iodine supplementation also show mixed results. Increasing incidence of thyroid cancer was noted following the halt of iodine supplementation in Poland,[137] although a study in Argentina found an increased incidence of papillary thyroid cancer following the addition of iodine to salt and a study in Sweden found similar temporal trends of PFC of the thyroid in areas with

high and low iodine intake.[138] Similarly, a study in Denmark did not observe differences in incidence by histologic type in high and low iodine regions.[139] In addition to iodine consumption, consumption of cruciferous vegetables (including cabbage, cauliflower, bok choy, and broccoli) that contain goitrogens has been thought to be related to cancer of the thyroid based on animal models.[140] However, a pooled case–control analysis of cruciferous intake and cancer of the thyroid did not report a positive association but rather a slightly protective effect among consumption of noncruciferous vegetables and cancer of the thyroid.[141] Environmental factors, including polyhalogenated aromatic hydrocarbons (PHAHs), particularly polybrominated diphenyl ethers (PBDEs), may be associated with cancer of the thyroid.[142]

Reproductive factors may also be associated with cancer of the thyroid; however, two recent cohort studies examining factors associated with estrogen levels that have been used in breast and gynecologic cancers, including parity, age at menarche, and age at menopause, do not support a relationship between female sex hormones and cancer of the thyroid.[143,144] Another cohort study did observe a positive association between late menarche and cancer of the thyroid but only for women <45 years old.[115] Case–control studies have reported associations between early and late age at menarche and parity with cancer of the thyroid[145,146]; however, these results are not consistent and a pooled analysis of case–control studies showed only a weak association.[147]

Descriptive Statistics

Incidence

Cancer of the thyroid is the most frequently encountered cancer of the head and neck in women with an incidence rate (15.84 per 100,000) that has increased substantially over time. The incidence of cancer of the thyroid has also increased throughout time for men; a more detailed discussion of these temporal trends and reasons for such trends will be featured later in this chapter. The age distribution for PFC is uniquely low compared to other cancers as the average age at diagnosis is ~46 years for women and 50 years for men.[2] The average age of diagnosis for medullary carcinomas is in the

early 50s for both males and females, and anaplastic carcinomas are typically not diagnosed until the late 60s for men and early 70s for women.[2]

Papillary and follicular cancer of the thyroid (PFTC) occurs more commonly in women compared to men with an incidence rate 2 to 3.5 times that of men, whereas the incidence of medullary and follicular carcinoma is similar for men and women. The female to male PFTC ratio is observed across race/ethnicities, with some variation, and across different continents including North America, Asia, and Europe.[148] The female to male ratio of PFTC also varies by age as ratio ranges from 5 to 6 for ages 20 to 29 and drops to 1 to 1.5 for 70- to 79-year-olds.[149] The converging incidence of male and female cancer of the thyroid with age has led to speculation that female sex hormones may contribute to cancer of the thyroid as mentioned earlier. Descriptive studies across several countries have noted these differences in the incidence of cancer of the thyroid for pre- and postmenopausal women; however, as mentioned above, the association between reproductive factors and cancer of the thyroid is equivocal.[147]

The incidence of cancer of the thyroid among females is over two and half times higher in developed (9.1 per 100,000 women) compared to developing countries (3.4 per 100,000 women). Within the United States, the incidence of cancer of the thyroid among non-Hispanic White women (19.4 cases per 100,000 women), Asians (17.9 per 100,000 women), and Hispanic females (16.4 per 100,000 women) are similarly high, and the incidence of black females (10.5 per 100,000 women) and American Indian/Alaska Natives (11 per 100,000 women) is lower. The lower incidence of cancer of the thyroid for Black and American Indian/Alaska Native women compared to non-Hispanic White is observed for each type of cancer of the thyroid except for anaplastic carcinomas.[149] As mentioned above, cancer of the thyroid is not common among men though the age-standardized incidence among men in developed countries is (2.9 per 100,000 men) is more than twice that of those in developing countries (1.1 per 100,000 men).[43] Among men, differences in incidence by race are less marked and range from 5.8 cases per 100,000 men for non-Hispanic Whites compared to 3.2 cases per 100,000 for Black men (see Table 4.1).

The lower incidence of PFTC among blacks is not fully understood and could be due to biologic or diagnostic reasons. The proportion of blacks

without health insurance is higher than that of whites[150] and they may be less likely to be diagnosed with smaller indolent cancers. Cases of cancer of the thyroid among blacks are more likely to be diagnosed at late stage at diagnosis and with larger size cancers.[151,152] Race/ethnicity is closely linked to SES, and studies have also noted a decreased incidence of cancer of the thyroid among residents residing in low SES census tracts[153] and those residing in counties with higher proportions of uninsured and non–high school graduates.[154] However, in a study of Kaiser Permanente health maintenance organization members, with presumably equal access to care, blacks had a lower incidence of cancer of the thyroid compared to whites.[155]

Hispanics are also more likely to be uninsured compared to non-Hispanic Whites; however, Hispanics have a similarly high incidence rate of PFTC as Whites. Hispanics who were born in the United States have incidence rates similar to Whites; however, Hispanics migrating to the United States have lower incidence rates.[156] Authors of this recent migrant study did not believe that the higher incidence of thyroid cancer among US-born Hispanic women is related to improved detection or overdiagnosis as the incidence of cancer of the thyroid has increased in other countries in the world.[156] Horn-Ross et al.[156] suggest that these differences could be due to variations in nutrient intake, specifically iodine intake, as well as reproductive factors.

Asian Americans have a similar incidence of cancer of the thyroid as White women in the United States. Among Asian Americans, Southeast Asian women, including Vietnamese, Filipino, and Cambodian, have higher incidence rates than do non-Hispanic White, Korean, Japanese, and Chinese American women.[157–159] A case–control study examining cancer of the thyroid among Southeast Asians observed an association between benign thyroid disorders and phytoestrogens including goiters, among patients with cancer of the thyroid.[160] Compared to their US-born counterparts, foreign-born Filipino and Chinese women have a lower incidence of cancer of the thyroid and foreign-born Japanese women have a higher incidence than do US-born Japanese women.[157]

Temporal Patterns

Papillary and follicular thyroid carcinoma has unequivocally increased in the United States; however, the temporal trends for other histologic types are less

clear. Follicular carcinoma increased for white and black male and females, whereas medullary carcinoma of the thyroid increased for white males. Additionally, the reasons for the increasing papillary carcinoma of the thyroid are not fully understood and the interpretations of increasing incidence rates are debated.[149,153,161–164] Several studies of the population-based SEER registry have documented increasing incidence of small cancers; however, increased incidence has been observed across all cancer sizes, including cancers ≥4 cm. Chen et al.[162] noted an 8.6% increase in cancer of the thyroid per year between 1988 and 2005 and a 5.7% increase in cancers ≥4 cm over the same time period (Fig. 4.11). Likewise, localized cancers have increased among men and women but so have distant-stage disease. Increases in the incidence of cancer of the thyroid have been detected across all race/ethnic groups but is more rapidly increasing among non-Hispanic Whites.[149] The detection of smaller cancers with ultrasonography and fine needle aspiration may account for some of the increasing incidence.[149,161,162] A European study noted an increasing incidence of cancer of the thyroid in regions with more cancer imaging[165] and US studies report a higher incidence of cancer of the thyroid among patients in higher SES zip codes.[151] Though papillary thyroid carcinoma has a good prognosis, the potential for overdiagnosis of cancer of the thyroid is important to consider given the unnecessary medical cost and emotional stress that comes with the treatment and diagnosis of cancer.

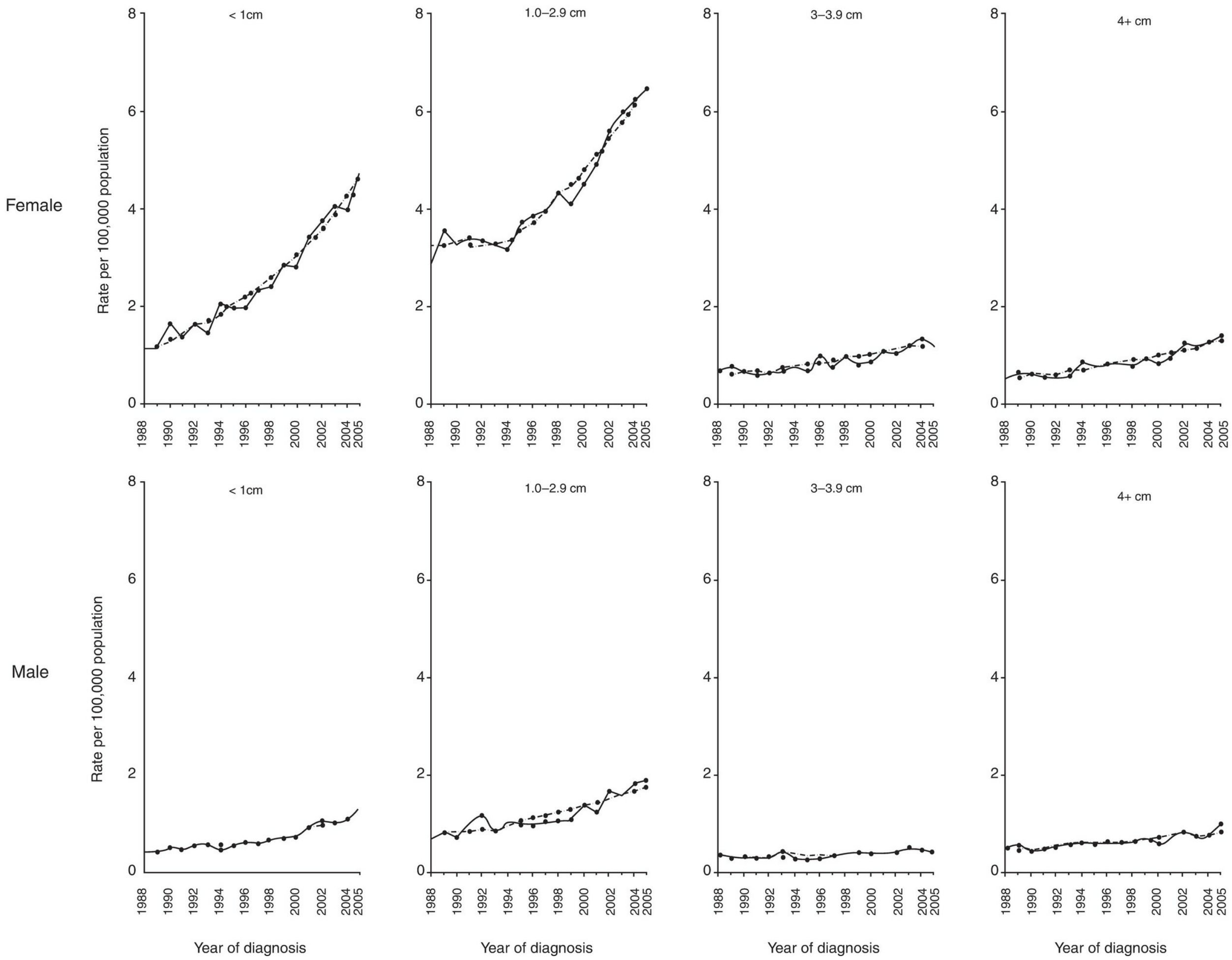

Figure 4.11. Incidence rates for cancer of the thyroid by diagnosis year, tumor size, and gender, SEER 1998–2005. (Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer*. 2009;115:3801–3807.)

The detection of small cancers is not the sole contributor to the increasing incidence of cancer of the thyroid due to the increasing incidence of larger and distant-stage cancers.[149,162,164] As mentioned above, radiation in childhood is a risk factor for cancer of the thyroid; however, there are no studies measuring average radiation in childhood over time. Additionally, environmental exposures, particularly PHAHs, PBDEs, may be associated with thyroid cancer.[142]

Prognosis

The large majority of PFCs are diagnosed with early-stage disease, whereas

approximately one-half of medullary carcinomas are diagnosed at a local stage, and only a small proportion (<10%) of anaplastic carcinomas are diagnosed with localized cancer. For PFCs, tumor size varies by race/ethnicity (Figs. 4.12 and 4.13). The proportion of blacks diagnosed with papillary carcinoma ≥4 cm is higher than that of whites. Hispanics also have a higher proportion of larger papillary carcinoma compared to Whites. The prevalence of follicular carcinomas ≥4 cm is lower than that for papillary carcinoma. Findings from the NCDB indicate that black patients were more likely to be diagnosed at a later stage compared to whites adjusting for several factors including insurance.[152] SEER summary stage by race/ethnicity are shown in **Figure 4.14**. Additionally, uninsured patients were more likely to be diagnosed at a later stage compared to privately insured, adjusted for race/ethnicity and other sociodemographic factors.[152]

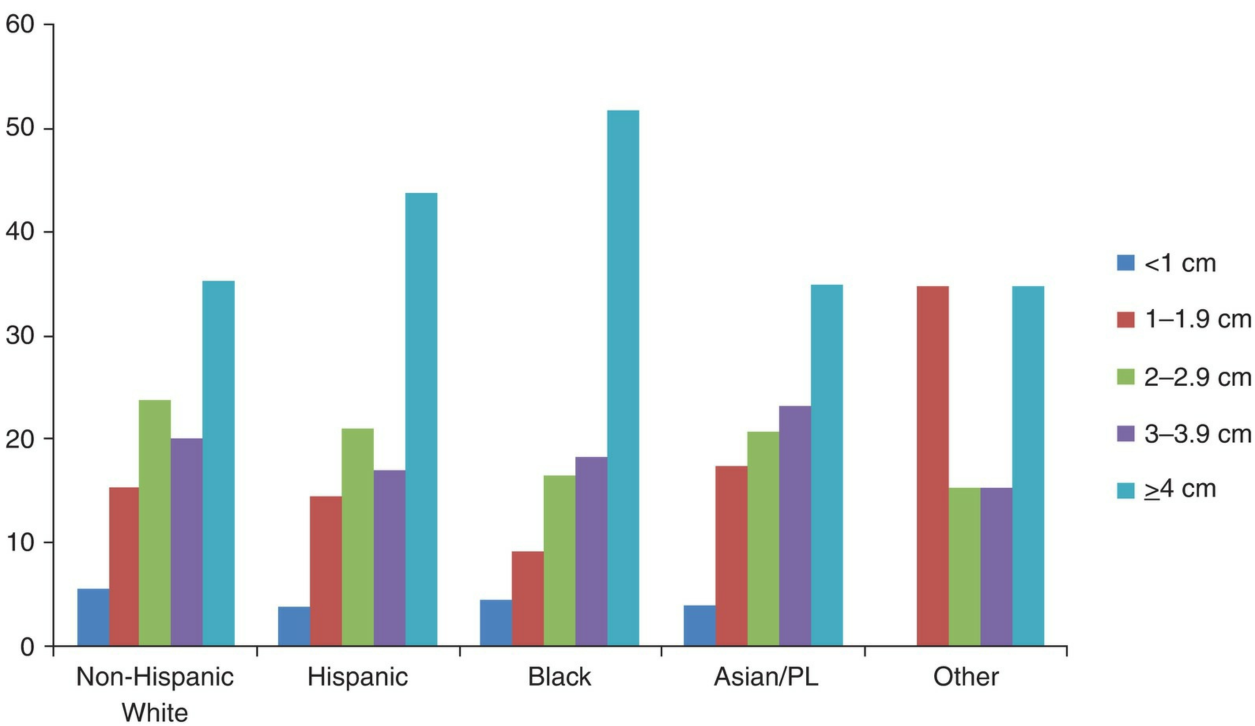

Figure 4.12. Distribution of papillary carcinoma of the thyroid by tumor size and race/ethnicity, SEER 18 2000–2009. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November

2012 submission. http://www.seer.cancer.gov)

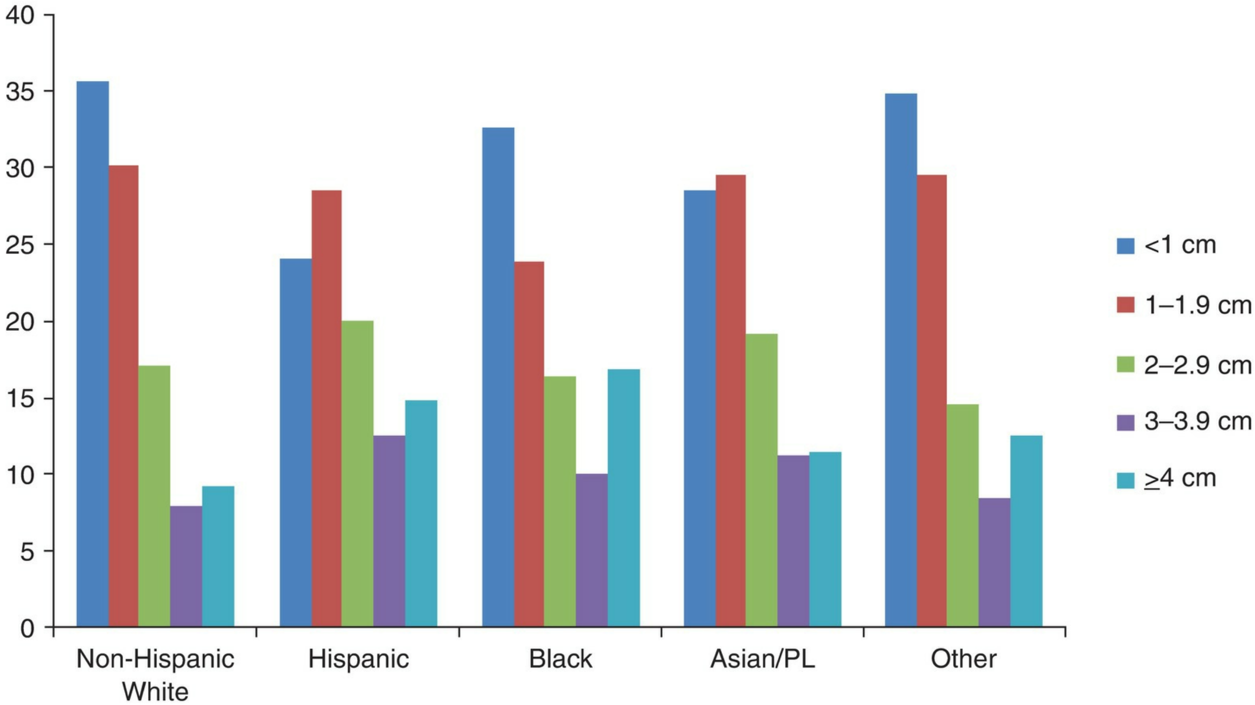

Figure 4.13. Distribution of follicular carcinoma of the thyroid by tumor size and race/ethnicity, SEER 18 2000–2009. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

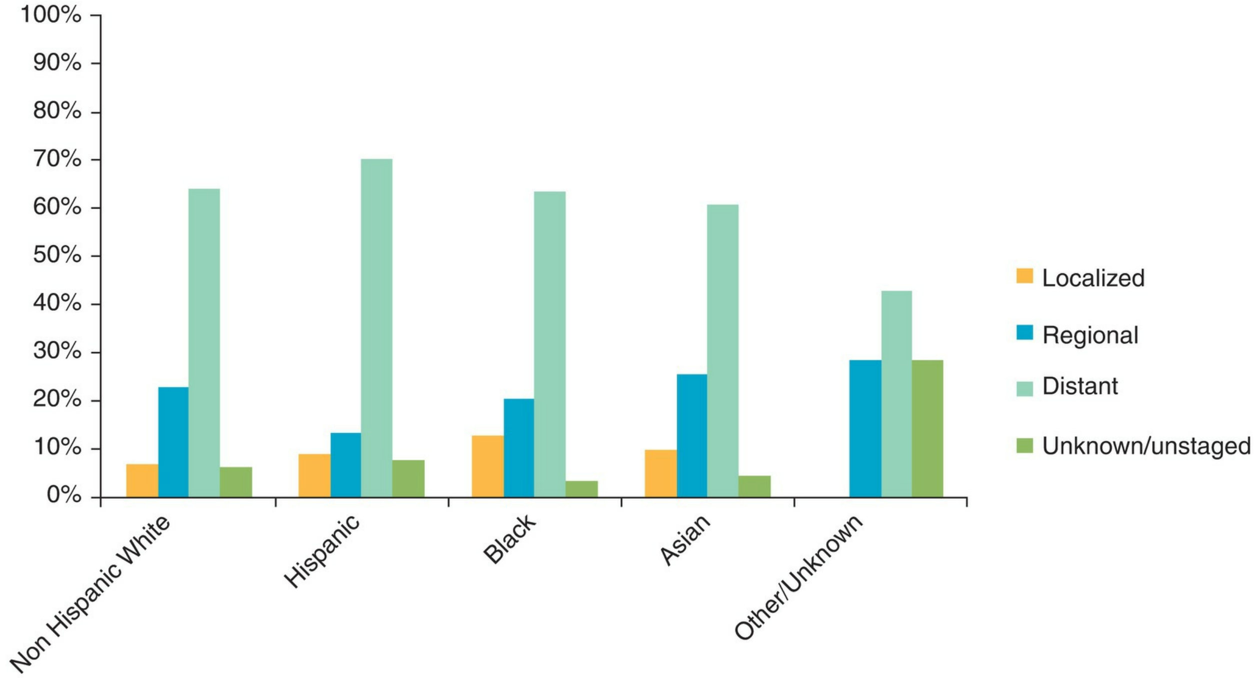

Figure 4.14. Distribution of anaplastic carcinoma of the thyroid by stage and race/ethnicity, SEER 18 2000–2009. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

As mentioned above, the 5-year survival for patients with PFC is drastically higher than medullary and anaplastic carcinoma as displayed in Figure 4.15. Survival differences among anaplastic carcinomas are difficult to assess given the rarity of the disease and overlapping confidence intervals of survival estimates. The 5-year survival among patients with medullary carcinoma varies from nearly 88% among Asians to 78.40% among Black; however, these differences are not significantly different due to overlapping confidence intervals. The 5-year relative survival for patients with follicular carcinomas is highest among Whites and Hispanics but slightly lower for blacks, and there are no discernible survival patterns by race/ethnicity for patients with papillary carcinoma. A study examining overall survival by race/ethnicity among all histologies of cancer of the thyroid noted increased observed survival among blacks compared to whites; however, after adjusting

for clinical factors, these differences diminished.[166]

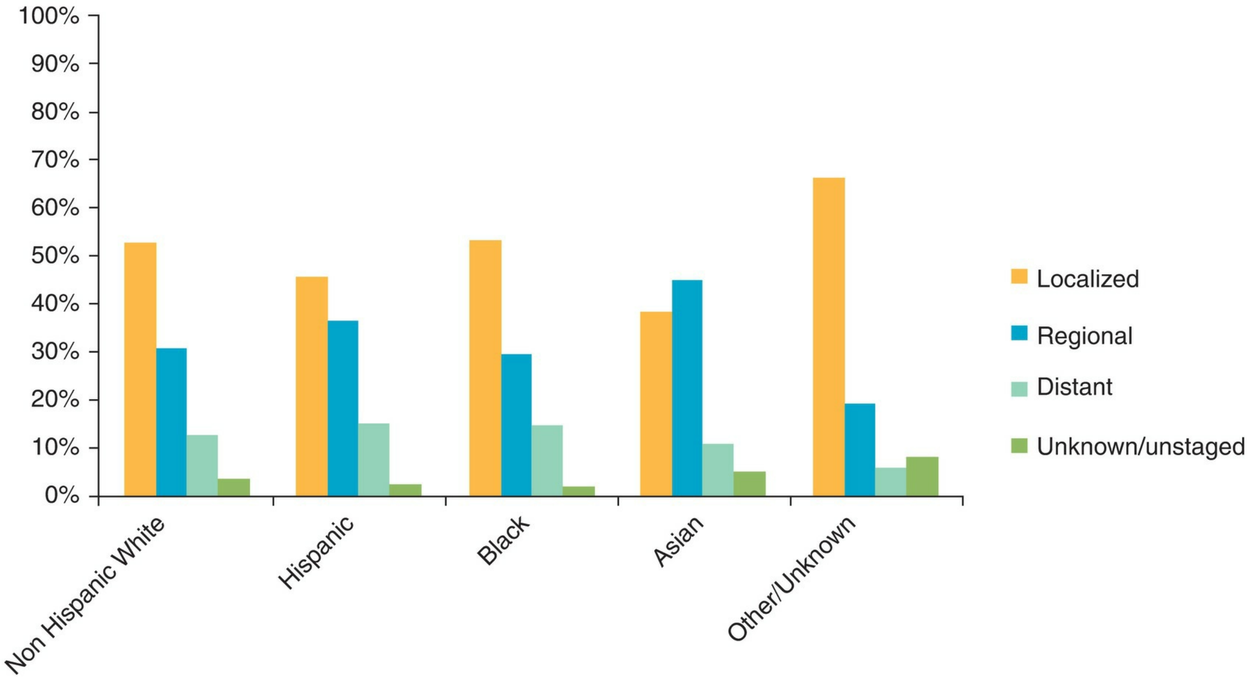

Figure 4.15. Distribution of medullary carcinoma of the thyroid by stage and race/ethnicity, SEER 18 2000–2009. (Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2011 Sub (1973–2010) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2010 Counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. http://www.seer.cancer.gov)

By gender, females have a slight survival advantage for papillary and follicular cancers, but not meaningfully different given the high survival for these cancers. A study of the National Thyroid Cancer Treatment Cooperative Study Group data suggested that survival differences by gender are modified by age where women diagnosed before the age of 55 had better survival rates than did men (HR 0.33, 95% CI 0.13 to 0.81) but experienced similar survival as men past the age of 55.[167] The high survival rate of patients with papillary carcinomas is observed for most ages where relative survival remains above 95% up until age 80 where it drops slightly to ~90%. Survival rates vary more obviously across age for follicular carcinomas where 5-year relative survival rates are over 99% for those patients under the

age of 50 and decrease to 85% among ages 70 to 79 and to 74% among cases 80 years and older. The 5-year survival rates for medullary carcinomas remain at around 80% to 84% before the age of 70 and decrease to 66% among those aged 70 to 79 and further decline to around 50% for those aged 80 years and older.

OTHER CANCERS OF THE HEAD AND NECK

Cancers of the Nasal Cavity and Paranasal Sinuses

Cancers of the nasal cavity and paranasal sinuses (NCPS) are rare. By subsite, the nasal cavity (44%) is the most common site followed by the maxillary sinus (33%), ethmoid sinus (9%), accessory sinus (4%), sphenoid sinus (3%), overlapping lesion of accessory sinus (2%), and frontal sinus (1%). About one-half of these are squamous cell carcinoma followed by adenocarcinoma (13%), epithelial cell carcinoma (9%), and melanoma (7%). The median age of diagnosis is 63 years.

There are several risk factors associated with cancers of the NCPS including occupational exposures, particularly to wood, nickel, and leather dust, which IARC concluded was sufficient evidence for carcinogenity.[58,168] Other occupational exposures that are probably or possibly carcinogenic include formaldehyde and textile dust.[58] Tobacco smoking is also a risk factor, and IARC deemed it a cause in 2002 with stronger associations observed for squamous cell carcinomas.[169,170] Environmental exposure to tobacco smoke has also been shown to be related to cancer of the NCPS as the risk of cancer is elevated among spouses of smokers.[171] Consumption of alcohol has not been consistently associated with cancer of the NCPS. At least two studies have shown a positive association between alcohol and NCPS,[171] whereas another has not.[172] Dietary factors including increased intake of fruit and vegetables have been associated with a lower risk of cancer of the NCPS, whereas salted and pickled foods are associated with higher risks.[171]

As mentioned above, the incidence of cancer of the NCPS is low as the age-adjusted incidence rate is ~0.7 cases per 100,000 in the United States.

The incidence among males is slightly higher (0.9 per 100,000) compared to females (0.6 per 100,000). Incidence increases markedly with age; the incidence among those <50 years of age is <1.0 per 100,000 and increases to 3.6 per 100,000 among those aged 85 years and older. Among males, the incidence is similarly low by race where whites, blacks, and other race incidence is 0.9, 1.0, and 1.0, respectively. Among females, incidence patterns do not vary by race; the incidence for whites, blacks, and others is 0.5, 0.6, and 0.6, respectively. Over time, the overall incidence of NCPS has remained stable at around 0.7 per 100,000 from 1975 to 2009.

Most patients with NCPS are diagnosed with localized- (29%) or regional-stage (55%) cancer and 17% are diagnosed with distant stage. Stage distribution varies by race; 31% of whites are diagnosed with localized disease compared to 19% of blacks and 15% of other races. The average 5-year relative survival is 53.5%; this varies greatly by stage where the survival rate is 80.8% for localized, 47.8% for regional, and 31.5% for distant-stage cancer. Survival also varies by race where the 5-year relative survival is 54.8%, 42.8%, and 51.2% for whites, blacks, and other races, respectively. The survival for NCPS has not varied significantly over time.

Sarcomas

Sarcomas of the head and neck are rare. The large majority of sarcomas of the head and neck (80%) are in the soft tissue whereas the remaining are in bone or cartilage.[173]Due to the rarity of the disease, there are limited data on the risk factors as well as incidence and prognosis. The histology of sarcomas of the head and neck is varied. Among 802 sarcomas of the head and neck diagnosed at the University of Texas MD Anderson Cancer Center between 1970 and 1999, the most common histologic type was osteosarcoma (14.6%) followed by malignant fibrous histiocytoma (11.2%), angiosarcoma (11.2%), and rhabdomyosarcoma (11.0%).[173] A relatively high proportion (17.6%) of sarcomas were unclassified, and neural, adipose tissue, and histogenesis unclear sarcomas were all rare. It is worth noting that histologic type also varies by age as rhabdomyosarcoma is much more common in children than adults whereas osteosarcomas are more commonly diagnosed in men and women between ages 30 to 40 years and the median age at diagnosis for liposarcoma is 50 years.[173,174] The most common site was the scalp and face (31.4%) and sinonasal tract (30.5%).[173]

Li-Fraumeni syndrome, which is a germline mutation on the p53 tumor suppressor gene, is associated with sarcoma.[175] Another inheritable mutation on Rb1 is also associated with sarcomas.[176] Exposure to radiation is also associated with sarcomas of the head and neck, though the postirradiation risk of sarcomas of the head and neck is low.[177–179] A single-institution study of 229 sarcomas of the head and neck noted that only 6% had a history of exposure to radiation and among cases with a history of radiation, there was an average 12-year latency period between radiation therapy and the diagnosis of sarcoma of the head and neck.[179]

Only 5% to 10% of sarcomas are in the head and neck, and an estimated 1,000 to 1,500 cases of sarcomas of the head and neck are diagnosed in the United States each year.[180] A single-institution study from Italy of 167 patients reported 19% and 11% of patients experience local recurrence and distant metastases within a 10-year period, respectively.[181] The disease-free survival was estimated to be 26% in the same 10-year period.[181] The 5-year survival reported by the Head and Neck Sarcoma Registry varies widely by histologic type as survival from chondrosarcomas and dermatofibrosarcoma was close to 100% whereas survival from osteosarcoma was <50% as well as rhabdosarcoma.[182]

Melanomas

Cutaneous melanomas occur all over the body and one study reported that the most common location of cutaneous melanomas was on the back for men and women under the age of 50 and the most frequent location among those aged 50 and older was on the head as well as the forearm.[183] The face is the most common site in the head and neck for melanomas to occur. Among cases with a known histology, lentigo maligna melanomas are the most common histologic type followed by Spitzoid malignant melanoma and nodular.[184] Mucosal melanomas also occur in the head and neck but are very rare and have different risk factors as well as incidence patterns compared to cutaneous melanoma.[185]

Total exposure to sunlight is associated with cutaneous melanoma; however, intermittent exposure is more strongly associated with melanoma.[186] Sunburns throughout one’s lifetime is also a notable risk factor for cutaneous melanoma; a review of 29 studies found increased odds of

melanoma with sunburns in adult life (OR = 1.91), adolescents (OR = 1.73), and childhood (OR = 1.95).[186] A pooled study of 15 case–control studies examining sun exposure by latitude, with varying levels of UV radiation, found no overall association between melanomas of the head and neck with recreational exposure.[187] This study did observe an association with occupational exposure, whereas other pooled results of all melanomas, including melanomas on the trunk, arm, head and neck, as well as other sites, did not observe an association between occupational sun exposure and occurrence of the melanoma.[186] Exposure to indoor tanning is also associated with melanomas and the risk of melanoma increases with the number of years, sessions, and duration of indoor tanning.[188]There is also a particularly strong association observed among those exposed to UVA-emitting devices.[188] Other individual characteristics, including fair skin and light hair as well as family history, and presence of asymmetric nevi, are also associated with the risk for melanoma.[189]

Most melanoma incidence patterns and figures include melanomas across all locations across the body. One study examining the incidence of melanoma by subsite estimated the incidence rate of 2.0 per 100,000 for men and 1.0 per 100,000 for women melanomas occurring on the face. Cutaneous melanoma is increasing in incidence, between 1999 and 2008; incidence increased by 2.1% and 2.4% per year among men and women in the United States across all sites, respectively.[190] The incidence of cutaneous melanoma across all sites, including the trunk, back, legs, as well as other extremities, varies significantly across race/ethnicity; the incidence rate of all melanomas is ~30 times higher in white males compared to black males and 20 times higher in white females compared to black females.[42] The incidence of melanoma for Whites is also higher than that of Asian and Hispanics. A study examining the incidence of melanoma in California by site reported that ~20% to 22% of melanomas were located on the head and neck for Whites, Hispanics, and Asians but only 12% for Blacks.[191]

Approximately 75% of cutaneous head and neck melanomas are diagnosed with stage I disease and 17%, 6%, and 2% are diagnosed with stage II, III, and IV disease, respectively.[192] Prognosis of cutaneous melanoma of the head and neck is generally high. Among cases diagnosed between 2004 and 2009 in the SEER database, cause-specific survival was

90.4% for females and 87.10% for males.[192] The hazard of death increases steeply with stage and increasing age.[192] Whites have a lower hazard of death (HR 0.60, 95% CI 0.47 to 0.77) after adjusting for stage, age, gender, as well as treatment.[192]

CONCLUSION

Cancer of the head and neck encompasses many sites including the oral cavity, pharynx, larynx, salivary glands, thyroid, sinonasal tract, and skin. Site and histology vary; some of these subsites share common risk factors and others do not. Smoking is a major risk factor for most cancers of the head and neck, particularly for cancers of the *oral cavity* and *larynx*, and HPV is a risk factor for squamous cell carcinoma of the *oropharynx*. Risk factors for *cancer of the salivary glands* are less well defined. Radiation exposure appears to be the strongest risk factor for cancer *of the thyroid*.

The risk factors for cancers of the head and neck vary by site (location); therefore, the incidence of cancers of the head and neck, as shown in Tables 4.1 and 4.2, varies markedly across sites, time, and gender. In this chapter, we have presented the incidence, prognosis, and survival and discussed risk factors for each site. Cancer of the head and neck is often considered as one site, but this group of cancers is heterogeneous in pathology, risk factors, incidence rates, and survival.

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5 Imaging of Head and Neck Cancer

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Over the past decades, there have been major advances and improvements in cross-sectional imaging techniques. Imaging, in particular computed tomography (CT), magnetic resonance imaging (MRI), and increasingly positron emission tomography (PET mainly combined with CT as PET/CT), now plays a central role in the management of head and neck cancer by the multidisciplinary team. Imaging can be used to identify tumor and at times suggest a differential diagnosis in order to attempt to distinguish benign from malignant lesions. However, in head and neck cancer, the determination of the specific tumor type requires biopsy for histopathology and increasingly molecular analysis, regardless of the imaging appearance of a tumor. Furthermore, not uncommonly, a diagnosis may have been already made at the time of initial imaging evaluation. Therefore, one of the most fundamental roles of imaging in head and neck cancer is to accurately determine the stage of a tumor and upstage the initial clinical assessment when appropriate. Imaging is integral in the evaluation of deep extent of tumor and lymph node levels that cannot be reliably evaluated clinically as well as in the identification of distant metastases. Following treatment, imaging is essential for surveillance and for identification of tumor recurrence, as well as for differentiating recurrence from treatment-related complications. The optimal imaging evaluation should focus on identification of tumor spread to critical structures that would alter tumor stage, determine resectability, and help with surgical and radiation therapy planning and approach.

This chapter provides an overview of current imaging modalities and emerging techniques for head and neck cancer imaging. It is neither the intention nor possible to cover such a broad topic in exhaustive detail in a single chapter. Rather, our aim is to introduce the most commonly used

techniques (CT, MRI, and PET/CT) and approach for noninvasive assessment of the common mucosal cancers of the head and neck. Imaging evaluation of sinonasal, oral cavity, oropharynx, hypopharynx, and laryngeal cancer will be discussed. A discussion of other cancer types and primary sites, including thyroid malignancies, salivary gland neoplasms, and skull base, is beyond the scope of this chapter. Ultrasound (US) and image-guided biopsies will be only briefly discussed. The chapter will begin with a discussion of the imaging techniques. This is followed by an overview of general assessment of tumors including tumor staging, spread, lymphadenopathy, and evaluation of perineural spread (PNS) of tumor. Post-treatment imaging will then be addressed. The chapter will conclude with primary site-specific considerations and a section on emerging imaging techniques.

IMAGING TECHNIQUES AND APPROACH TO HEAD AND NECK CANCER

Overview

Cross-sectional imaging techniques such as CT and MRI are the mainstay anatomic imaging modalities used for initial evaluation and follow-up of head and neck cancer. Since its invention in the 1970s, there have been remarkable advances in speed of acquisition and quality of images generated by CT scanners. MRI is another robust imaging technique that provides superb soft tissue contrast and likewise has undergone significant technical improvements enabling high-quality imaging of head and neck cancer and intracranial tumor extension. While both techniques have their strengths, currently, CT is typically the first-line imaging modality for initial evaluation of most head and neck pathologies. One exception is imaging of nasopharyngeal carcinoma (NPC), in which MRI has been shown to be superior in tumor staging,[1–6] although there can still be significant practice variations among different institutions. This will be discussed in greater detail later in the section on the nasopharynx. MRI also has certain advantages in the evaluation of sinonasal and oral cavity tumors that will be discussed in the specific sections on these primary sites. MRI is frequently used as an

adjunctive imaging modality for additional assessment of equivocal findings on CT, and has specific advantages for the evaluation of PNS and intracranial extension of tumor and is complementary to CT for evaluation of bone invasion.

Another important milestone in head and neck cancer imaging has been the introduction of molecular imaging techniques. PET, combined with anatomic/morphologic imaging techniques like CT (and more recently MRI), has emerged as an important adjunctive tool for initial evaluation and follow-up of head and neck cancers. US plays a central role in evaluation of thyroid disease, including thyroid malignancies, and is an important adjunct imaging tool in the assessment of nodal disease, particularly with its ability to facilitate image-guided biopsies. However, beyond select applications, US is not routinely used for evaluation and follow-up of the majority of mucosal head and neck malignancies in most North American institutions. Plain films and fluoroscopy have little role in routine evaluation and follow-up of head and neck cancer. The use of videofluoroscopic techniques for evaluation of swallowing and dysphagia in patients with head and neck cancer is beyond the scope of this chapter. The chapter will begin with an overview of CT, MRI, and PET before proceeding to a more specific discussion of tumor assessment.

Computed Tomography

Overview of CT Image Acquisition

CT is the first-line imaging modality for evaluation of most head and neck cancers in adults, known or suspected. Although it is not necessary to understand the complex physics and informatics behind acquisition of a CT scan, familiarity with broad principles behind image acquisition and display will enable a more effective use of the technology and recognition of its limitations. CT images are generated when x-rays transmitted through the patient's body are processed by detectors and reconstructed into a tomographic image, or slice, using sophisticated computer algorithms. The current conventional state-of-the-art CT scanners have a rotating gantry with a tube and detector opposing each other and enable acquisition of multiple slices simultaneously.[7] Current state-of-the-art scanners typically are 64-slice or higher, and the typical 64-slice scanner can generate slices with a thickness

of as little as 0.5 to 0.625 mm. For the standard neck CT, images should be typically reconstructed at a section thickness between 1 and 3 mm. The spatial resolution of the images in the axial (X to Y) plane, that is, the ability to resolve fine detail or the smallest distance at which two separate objects can be distinguished on an image, ranges between 0.33 and 0.47 mm. Because of their high resolution, the axial acquisitions on modern CT scanners can be used to generate "reformatted" images in the coronal and sagittal planes. This can be very useful for evaluation of head and neck cancer. In addition to the improvements in image quality, technical advances in CT have also resulted in significantly reduced patient exposure to ionizing radiation on modern CT scanners compared to their earlier counterparts.

Tissue Characterization and Image Display in CT

On CT, different tissues are characterized and distinguished based on their ability to attenuate x-ray beams passing through. The density of a structure can be quantified, and the standard measure used for quantification is the Hounsfield unit (HU), named after the British engineer who built the first CT scanner in the 1970s. By convention, the attenuation of x-rays by water is used as a standard reference and arbitrarily set at 0 (zero) HU. All other attenuations are reported in reference to that of water. The basic densities typically used as reference points on CT are air, fat, water, soft tissue, and bone, each having a higher attenuation (i.e., density or brightness) than the preceding, respectively (Fig. 5.1; Table 5.1), spanning a range of densities typically between −1,000 and +3,000 HU. Increased iodine content of a tissue also results in increased density of that tissue, which forms the basis of contrast-enhanced CT images.

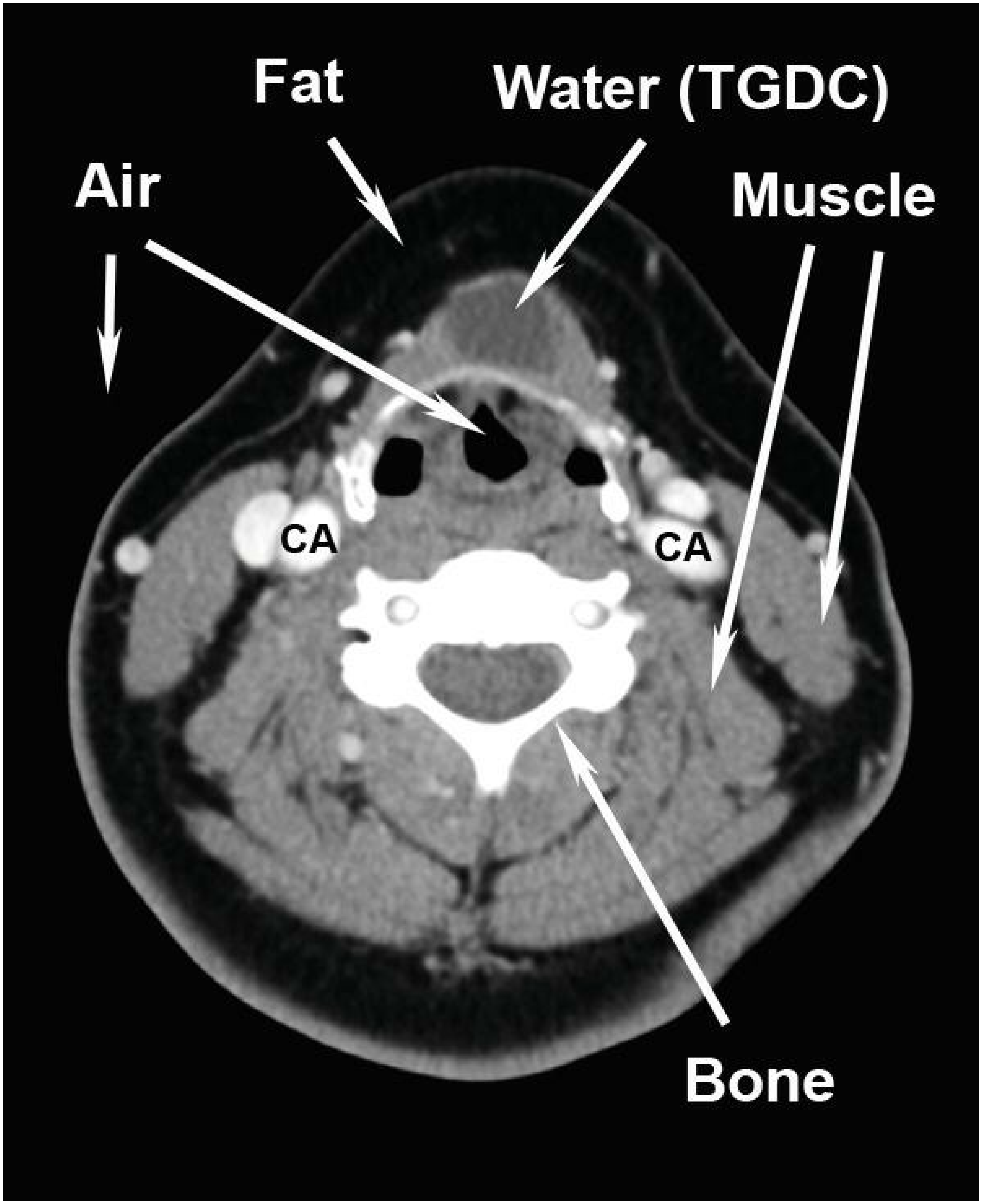

Figure 5.1. Axial contrast-enhanced CT image from a patient with a thyroglossal duct cyst (TGDC) demonstrates the basic tissue densities on CT. As discussed in greater detail in the text, there is progressively increasing density of air (*dark black*), subcutaneous fat, fluid or water (within the TGDC), muscle (soft tissue), and bone. Various intermediate densities are

seen, such as the brightly opacified carotid arteries (CA), secondary to a higher concentration of intravenous iodinated contrast, with density much higher than muscle but less than bone.

Table 5.1 Basic Tissue and Tumor Characteristics on Contrast-enhanced CT

Tissue or Lesion	Relative Density and Approximate Hounsfield Unit (HU) Measurement	Comments
Air	Dark black; –1,000 HU range	
Fat	Darker than fluid; –180 to –30 HU	Macroscopic fat has a distinctive appearance and is readily recognized on CT. Fat is an important source of "intrinsic contrast," readily distinguishable from normal soft tissues such as muscle and most (nonlipomatous) tumors.
Water and other simple fluids	–30 to +20 HU	Simple cystic lesions, such as thyroglossal ducts cysts, have this density. However, areas of cystic change and necrosis within a tumor or lymph node can also approach the density of water on CT.
Normal soft tissues (e.g., muscle), tumor, complex fluid or cystic lesions (i.e., proteinaceous or hemorrhagic)	Typically +20 HU to +70/+100 HU; may be as dense as +300 HU or higher	Most tumors and soft tissues have densities less than +100 HU on contrast-enhanced CT. However, very vascular tumors (e.g., paraganglioma) with large iodine content can have higher density. Vessels with high iodine content can approach or even exceed +300 HU depending on the phase of the study, for example, in angiographic studies.
Bone, metal implants	Range close to +3,000 HU or higher for metal implants	Bone is very dense on CT, and this further varies based on the type of bone (i.e., cortical bone is denser than cancellous bone). Metallic devices can be even denser than bone, exceeding +3,000 HU, and appear very bright on CT.

On CT, tissue density can be quantified, measured by its Hounsfield unit (HU) density value. By convention, the attenuation of x-rays by water is used as standard reference and arbitrarily set at 0 (zero) HU. Greater HU value indicates greater density or brightness on CT.

Air essentially does not attenuate x-ray transmission and would have densities in the −1,000 HU range, appearing black on a CT image displayed with soft tissue settings, or "window" (discussed further below) (Fig. 5.1). Fat typically has densities between −180 and −30 HU and visually appears black on soft tissue "windows." Water and other simple fluids have densities ranging between −30 and +20 HU. More complex (i.e., proteinaceous or hemorrhagic) fluid and soft tissue (in the absence of IV contrast) have densities higher than +20 HU and may approach densities up to +70 to +100 HU. However, after administration of IV iodinated contrast, these could have densities as high as +300 HU, particularly in a structure with a high concentration of contrast such as a vessel (Fig. 5.1), if properly timed. Bone is very dense on CT, and the density further varies based on the type of bone

(i.e., cancellous vs. cortical bone) and can have attenuations of up to +3,000 HU.

To recapitulate, the ability to distinguish both normal and pathologic structures on CT is based on their density/attenuation. Therefore, spaces or tissues with largely different densities, such as soft tissue tumor invading a normally fat containing area or tumor extension into air containing sinus, are easy to distinguish on CT. However, this “inherent” tissue contrast by itself is insufficient for optimal imaging of head and neck cancer. The reason is that proper staging of tumor extent and lymphadenopathy frequently requires distinction from adjacent soft tissues, such as muscle, which can have very similar density to tumor on an unenhanced CT scan (Fig. 5.2). Therefore, in order to improve soft tissue contrast and help distinguish tumor from normal soft tissues or vital structures such as vessels, neck CTs are almost always performed after administration of iodinated IV contrast unless contraindicated. Administration of iodinated contrast agents results in increased tissue contrast and improves detection and delineation of tumors based on differences in their composition and vascularity, resulting in different enhancement patterns compared to normal soft tissue structures (Figs. 5.2 and 5.3). Sometimes, there can be early or increased enhancement of the tumor margins, presumably because of the higher vascularity of the tumor periphery[8] (Fig. 5.3). There is no need for routinely obtaining a precontrast study before the contrast-enhanced scan. However, a second set of contrast-enhanced images in a plane with a slightly different angle should be obtained through the oral cavity to improve visualization of areas obscured by dental artifact on the standard acquisition. Absolute and relative contraindications to the use of IV iodinated contrast agents are most frequently due to a history of allergic reactions or impaired renal function, a more detailed discussion of which is beyond the scope of this chapter.

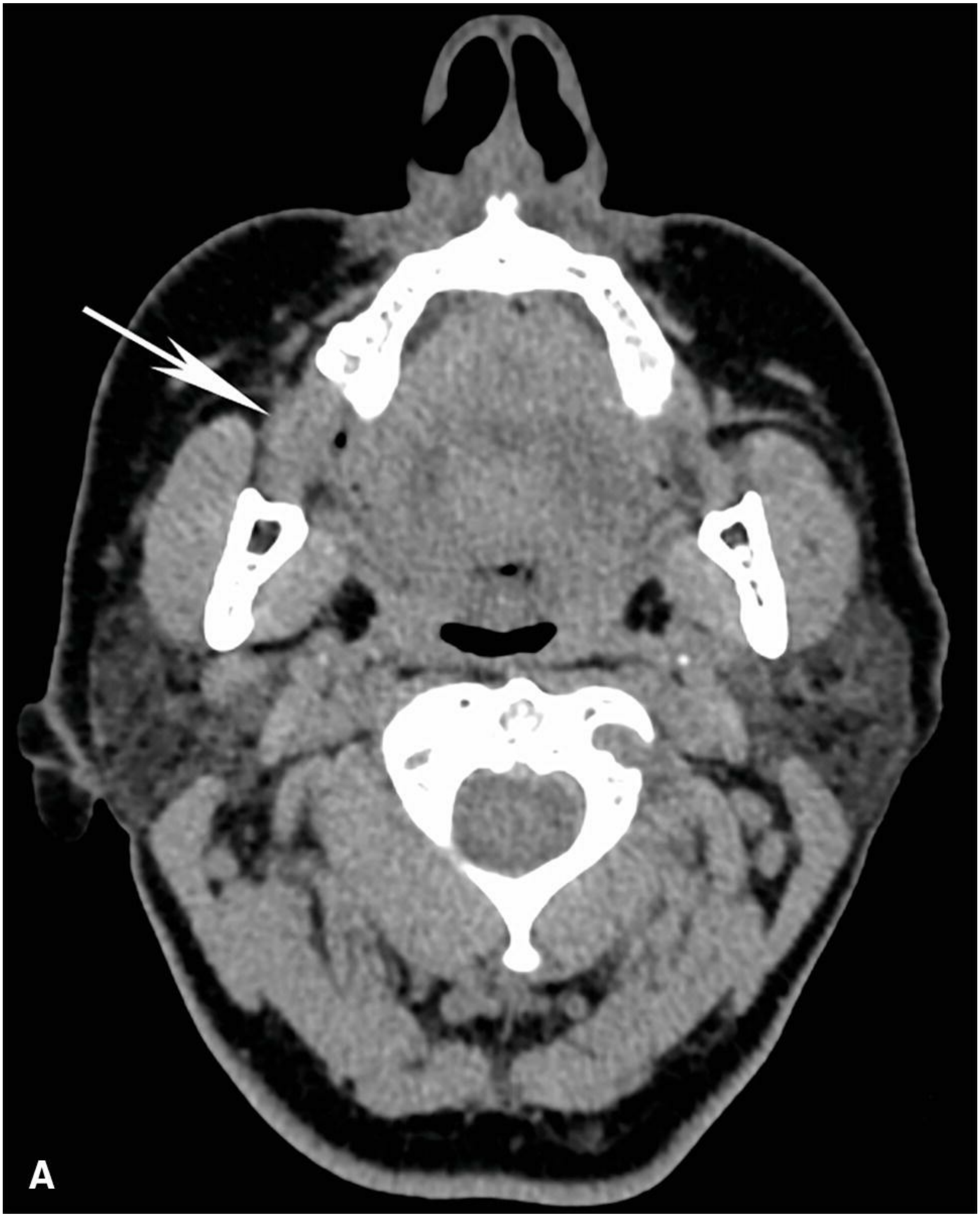
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Figure 5.2. Contrast-enhanced neck CT for tumor evaluation. Axial CT images obtained **(A)** before and **(B)** after administration of IV contrast from a 59-year-old woman with a right buccal squamous cell carcinoma (*arrow*) are

shown. **A:**Without IV contrast, there is asymmetry at the site of tumor, but the density is nearly identical (isodense) to muscle, and it is very difficult to clearly visualize the tumor margins. **B:** After administration of IV contrast, there is differential enhancement of tumor compared to adjacent soft tissues with better delineation of tumor margins.

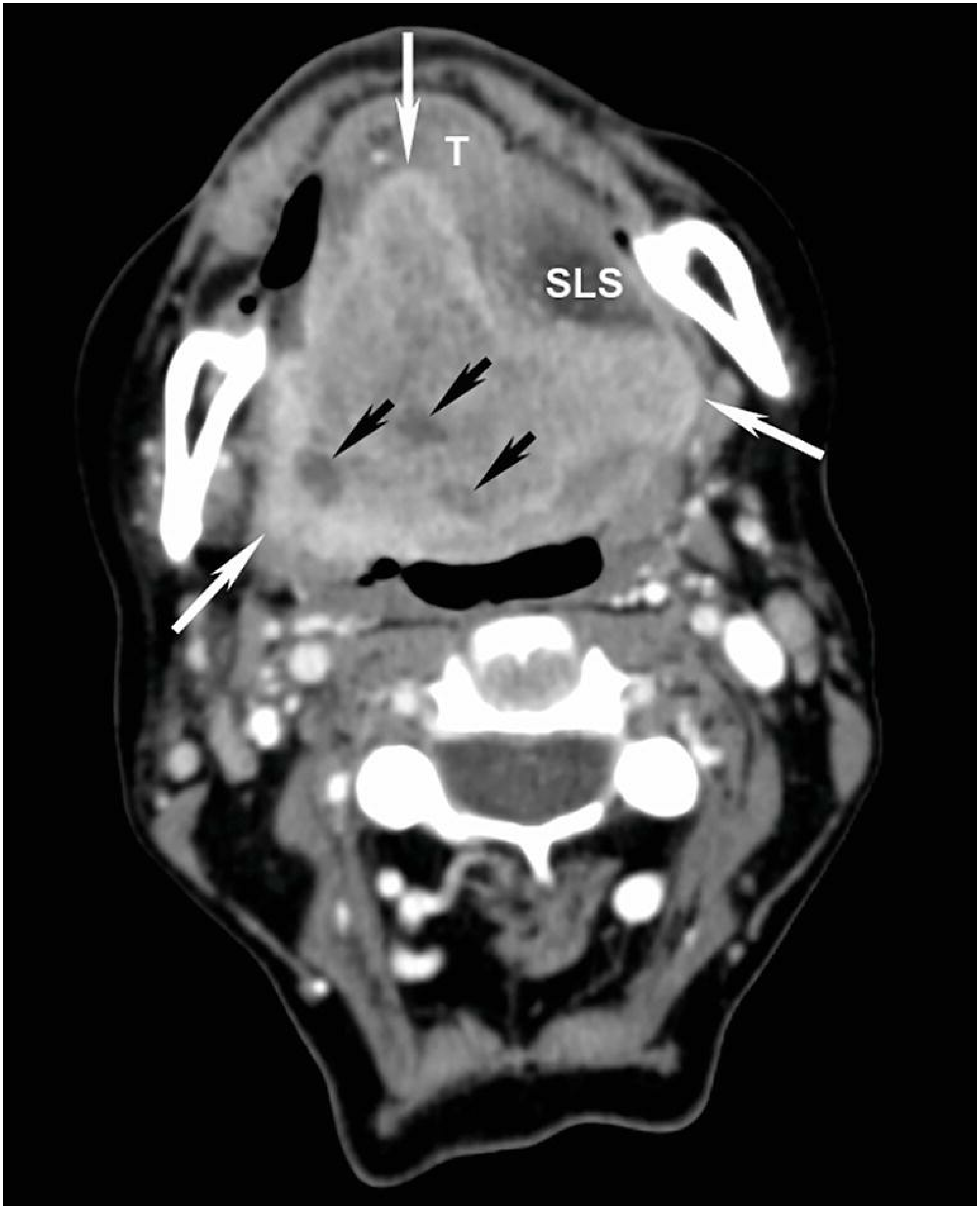

Figure 5.3. Contrast-enhanced neck CT for tumor evaluation and delineation. Axial contrast-enhanced CT image from a 56-year-old woman with a large invasive oral tongue cancer is shown. Because of differences in tumor vascularity compared to normal tissues, contrast-enhanced images are used to

distinguish tumor from otherwise similar density soft tissues such as muscle. Note the clear demarcation of the enhancing edge of tumor (*white arrows*). The small low-density areas within the tumor represent areas of cystic change and necrosis (*small black arrows*). T, tongue muscles; SLS, sublingual space.

Clinicians should be aware that for optimal viewing of specific structures, different display parameters, referred to as “windows,” are used. Windows routinely used during evaluation of a neck CT include soft tissues, bones, and lung windows (because the lung apices are scanned as part of standard neck acquisition). Failure to use the proper window may result in overlooking an abnormality. For example, failure to use bone windows may result in overlooking bone invasion (Fig. 5.4) or a bone metastasis. Commonly used display windows are also usually preprogrammed using different function keys for easy and rapid access.

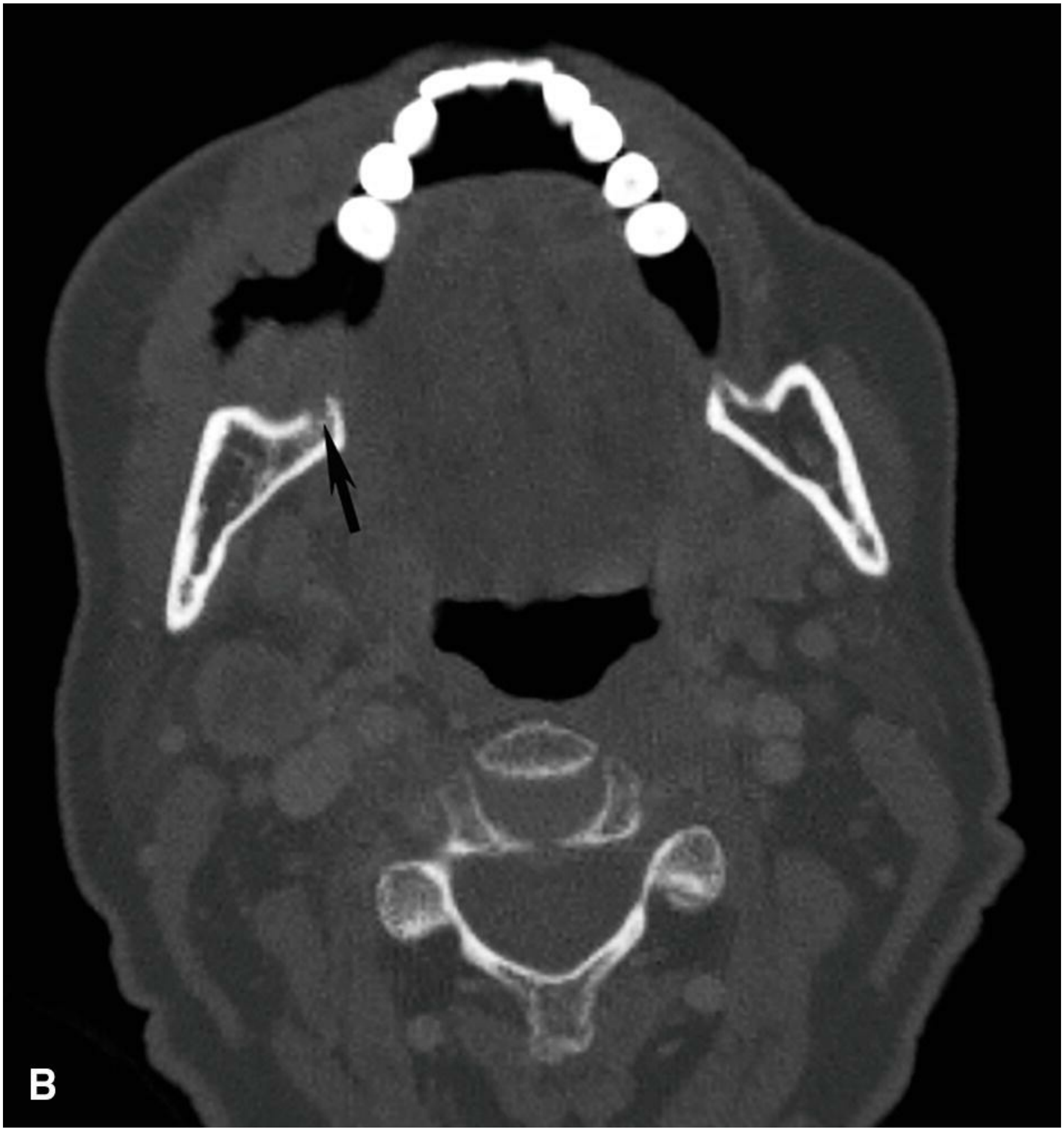

Figure 5.4. Optimal window display for evaluation of bones on CT. Axial contrast-enhanced CT images are shown from a 67-year-old woman with squamous cell carcinoma of the right gingivobuccal sulcus with extension to the retromolar trigone. The same slice is shown using two different reconstruction algorithms and display windows. **A:** Image displayed using narrow soft tissue windows is used for demonstration and evaluation of the mass (*white arrows*) and adjacent soft tissues. Notice how the cortex of the mandible is very bright when displayed in soft tissue windows with poor

visualization of bone architecture (*black arrow*). This image is not diagnostic of cortical invasion. **B:** The same slice reconstructed and displayed in bone "algorithm" demonstrates a small defect (*arrow*) corresponding to a pathologically proven focal cortical invasion of the mandible, resulting in a T4 stage designation. Note that although the bone windows demonstrate cortical invasion to better advantage, the soft tissue mass itself is poorly seen using these display parameters.

Magnetic Resonance Imaging

Basics of MRI

Whereas CT relies on differences in attenuation of x-ray beams by different tissues and tumor for distinction, MRI relies on entirely different properties of tissues. MRI is a powerful imaging technique based on the application of a uniform external magnetic field coupled with use of radiofrequency (RF) excitation pulses. Placement into an external magnetic field results in alignment of some of the protons within the tissues of the body. An RF pulse is then applied to perturb and result in a change in alignment of some of those protons, which subsequently return to their original alignment upon discontinuation of the RF pulse. This process produces signals that are ultimately reconstructed into images. Using different parameters, multiple "sequences" are acquired, each demonstrating different tissue characteristics and typically in different planes. These are then interpreted for characterization of normal tissues and pathology.

In general, MRI has superb soft tissue contrast that is superior to CT. Therefore, although CT provides an excellent evaluation of most head and neck cancers, in certain cases MRI may be able to identify tumor not seen on CT (Fig. 5.5). However, one disadvantage of MRI for head and neck cancer imaging is the relatively long scan times of at least 20 to 30 minutes or longer. Patients with head and neck cancer may have difficulty undergoing an MRI because of their inability to handle secretions and remain motionless during the scan, decreasing the diagnostic quality of the examination. This results in increased propensity to motion artifact, particularly below the hard palate, where there can also be image degradation secondary to swallowing artifact. A more detailed comparison of the two techniques will be provided later.


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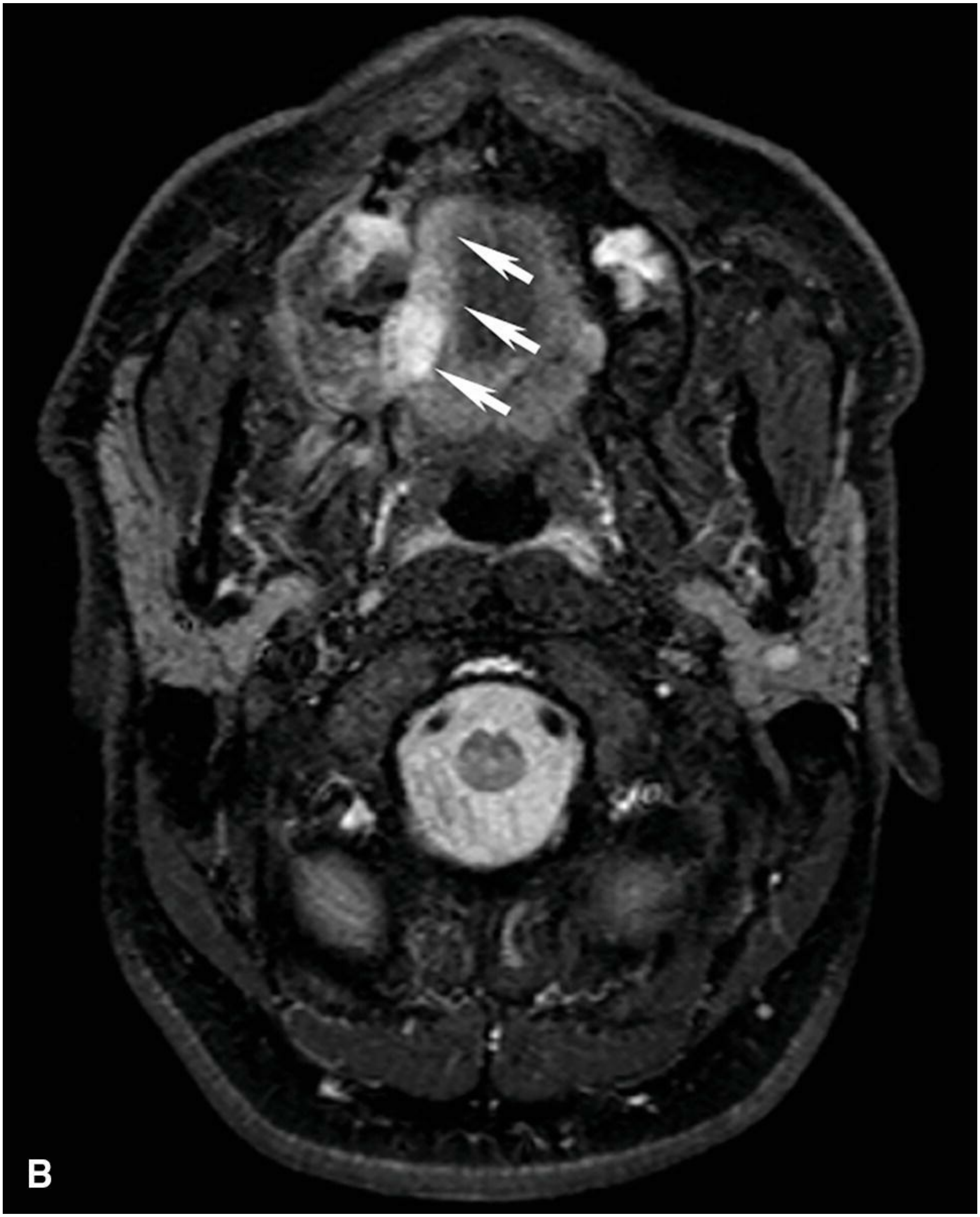
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Figure 5.5. Superior soft tissue contrast of MRI compared to CT. Axial CT **(A)** and MRI **(B, C)** images are shown from a patient with an adenoid cystic carcinoma involving the right hard palate. On the contrast-enhanced CT

image, the approximate area of the lesion is marked by the *arrows*. The lesion is not clearly visible on CT, and only mild asymmetry and minimal heterogeneous density are seen in the region of the tumor. STIR **(B)** and contrast-enhanced T1w fat-suppressed MR images **(C)**, on the other hand, demonstrate abnormal high signal and heterogeneous enhancement in the right hard palate (*arrows*, **B** and **C**, respectively). Although CT typically enables excellent tumor delineation, occasionally, such as in this case, the lesion is much better seen on MRI because of MRI's superior soft tissue contrast.

There are trade-offs between key parameters affecting the quality of a scan and length of acquisition, which can both positively and negatively affect image quality. This is particularly relevant for MRI given the long scan times. Spatial resolution (e.g., when high-resolution imaging is required to look at a small structure of interest such as skull base neural foramina) comes partly at the expense of signal-to-noise ratio and ability to evaluate soft tissue contrast (i.e., ability to distinguish tumor from adjacent normal soft tissues), unless the duration of acquisition of a sequence is increased. However, while increasing the length of a scan improves signal to noise, it also predisposes to motion artifact, which can degrade image quality. Therefore, the MRI protocols are designed carefully and optimized to achieve the best result taking into account these variables. When detailed evaluation of a small area of interest, such as skull base foramina, is required, this is best performed as a targeted exam focusing on the area of interest, rather than an evaluation of the entire neck, if possible. An optimal examination is designed to achieve reasonable scan times that can be tolerated by the patient and also enable acquisition of high-quality images without significant motion degradation and image distortion.

Basic Sequences Used for MRI and Evaluation of Tissue Signal Characteristics

As discussed earlier, an MRI examination consists of different "sequences," typically obtained in different planes. Unlike CT, MRI of head and neck cancer is obtained without and with administration of IV contrast. For MRI, paramagnetic gadolinium (Gd)-based contrast agents are used, different from iodinated contrast agents used in CT. The basic sequences that can be used

for head and neck imaging are T1-weighted images (T1w), T2-weighted images (T2w), and short tau inversion recovery (STIR) images. T1w and T2w images can be obtained with fat suppression (T1FS and T2FS) to suppress the bright signal of fat and highlight pathologies such as tumor (see below for more explanations). T1w/T1FS or similar type sequences are used for evaluation of enhancement characteristics of a tumor, because Gd-based MRI contrast agents result in signal change and appear bright (white in color, or "hyperintense") on these sequences. It should be noted that the names and certain technical parameters for the sequences can vary depending on the specific scanner and vendor.

On MRI, lesions are characterized based on their signal or brightness. Lesions with higher signal are described as "hyperintense," those with signal similar to a reference structure are described as "isointense," and those with lower signal than the reference are described as "hypointense." The signal is typically compared to a standard or specific structure of interest. The reference used varies depending on body site (or the reader may specifically select a reference for comparison when appropriate), but in head and neck, the standard reference is frequently muscle. The typical sequences used for MRI evaluation of the neck and tissue and tumor characteristics on these sequences are summarized in Table 5.2 and are also further discussed below. Other sequences, such as head and neck applications of diffusion-weighted imaging, will be discussed in the section on emerging techniques.

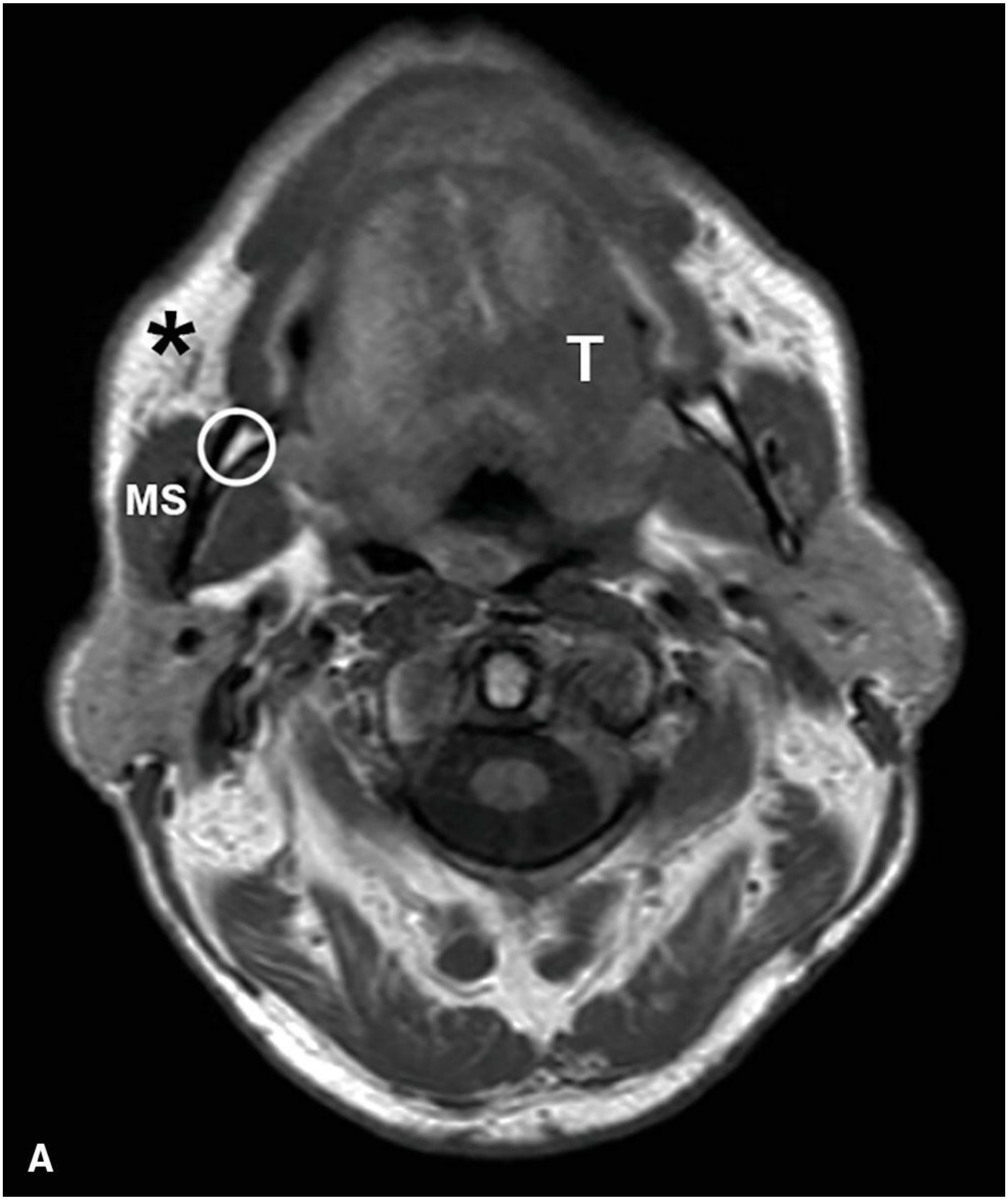
Table 5.2 Basic MRI Sequences and Tissue Characteristics

Sequence	Basic Tissue Signal	Comments
T1w, without fat suppression	High signal: fat (including fat in the bone marrow), paramagnetic contrast, subacute hematoma (methemoglobin), mineralization	Good for depicting tissue architecture and anatomy. Enhancing tumor not as conspicuous as T1w images with fat suppression
	Intermediate signal: muscle, tumor	Fat can act as intrinsic contrast agent and help identify invasion of fatty structures by tumor by demonstrating replacement of high signal fat by intermediate signal of tumor
	Low signal: fluid, edema (low to intermediate)	Necrotic part of tumor or lymph node would have lower signal approaching that of fluid
	Very low signal/dark black: cortical bone, calcium	Hemorrhage or proteinaceous fluid can be bright—compare with precontrast images in order not to misinterpret as tissue enhancement
T1w, with fat suppression (standard sequence used to evaluate enhancement characteristics of tissues and tumor)	Fat has low, dark signal. Although not identical, other tissue signal patterns generally follow the trends described for T1w image without fat suppression.	Used to evaluate tumor enhancement, appearing as increased signal Better demonstrates tumor enhancement and allows clearer distinction from bright signal of normal structures such as fat
		Always compare to precontrast images to make sure bright signal is true enhancement (and not increased signal from proteinacious secretions and content or hemorrhage)
		Longer acquisition time than non–fat-suppressed T1 images may increase propensity to motion artifact
		Increased propensity to susceptibility artifact (at interfaces between air-containing paranasal sinuses and bones at the skull base or dental filling and implant artifact)
		Inhomogeneity of fat suppression can occur and should not be misinterpreted as bright signal from abnormal enhancement
		Enables diagnosis and confirmation of lesions with macroscopic fat content (e.g., a dermoid or lipoma or fat within a liposarcoma)
T2w images (fast spin-echo technique)	High signal: fluid, edema, fat (but less bright than fluid and not as bright as fat on T1w images)	Fat-suppressed T2w images accentuate high signal of tumor and edema by suppressing the bright signal of fat
	Intermediate signal: muscle (intermediate to low signal)	There may be areas of inhomogeneous or incomplete fat suppression (particularly superficially or in areas prone to susceptibility): should not be misinterpreted as abnormal
	Very low signal/dark black: cortical bone, calcium	Tumor usually has intermediate to high signal, and this sequence typically provides good contrast between tumor and muscle
		Higher cellularity tightly packed tumors may have relatively lower signal than lower cellularity loosely packed tumors
		Reactive tumor-associated edema typically appears brighter than the tumor itself
		Distinction from other structures such as salivary gland tissue may not be as clear based on signal alone and requires evaluation of subtle detailed anatomic features and/or correlation with other sequences
STIR	Although not identical, tissue signal patterns generally follow the trends described for fat-suppressed T2w images.	Typically has lower signal-to-noise than fast spin-echo T2w images, but practically, that is compensated for by greater soft tissue contrast and more uniform suppression of bright fat signal
	Fluid is even brighter than on T2w images.	Very good sequence for demonstrating tumor-associated edema or edema secondary to denervation change; see above comments and caveats for T2w images

T1w Images and Contrast-Enhanced Imaging.

T1w images can be performed without or with fat suppression and are also the sequences used for evaluation of contrast enhancement as described earlier. Standard, non–fat-suppressed T1w images have relatively short scanning times and are good for evaluating normal anatomy and tissue

architecture (Fig. 5.6). On this sequence, fat is very bright, muscle has intermediate signal, and simple fluid has low signal. Cortical bone has a very dark signal. The signal of the medullary portion of bones varies depending on the extent of their fat and hematopoietic elements. Fatty marrow appears bright, whereas significant cellular infiltration of marrow, including marrow invasion by tumor, has intermediate signal.



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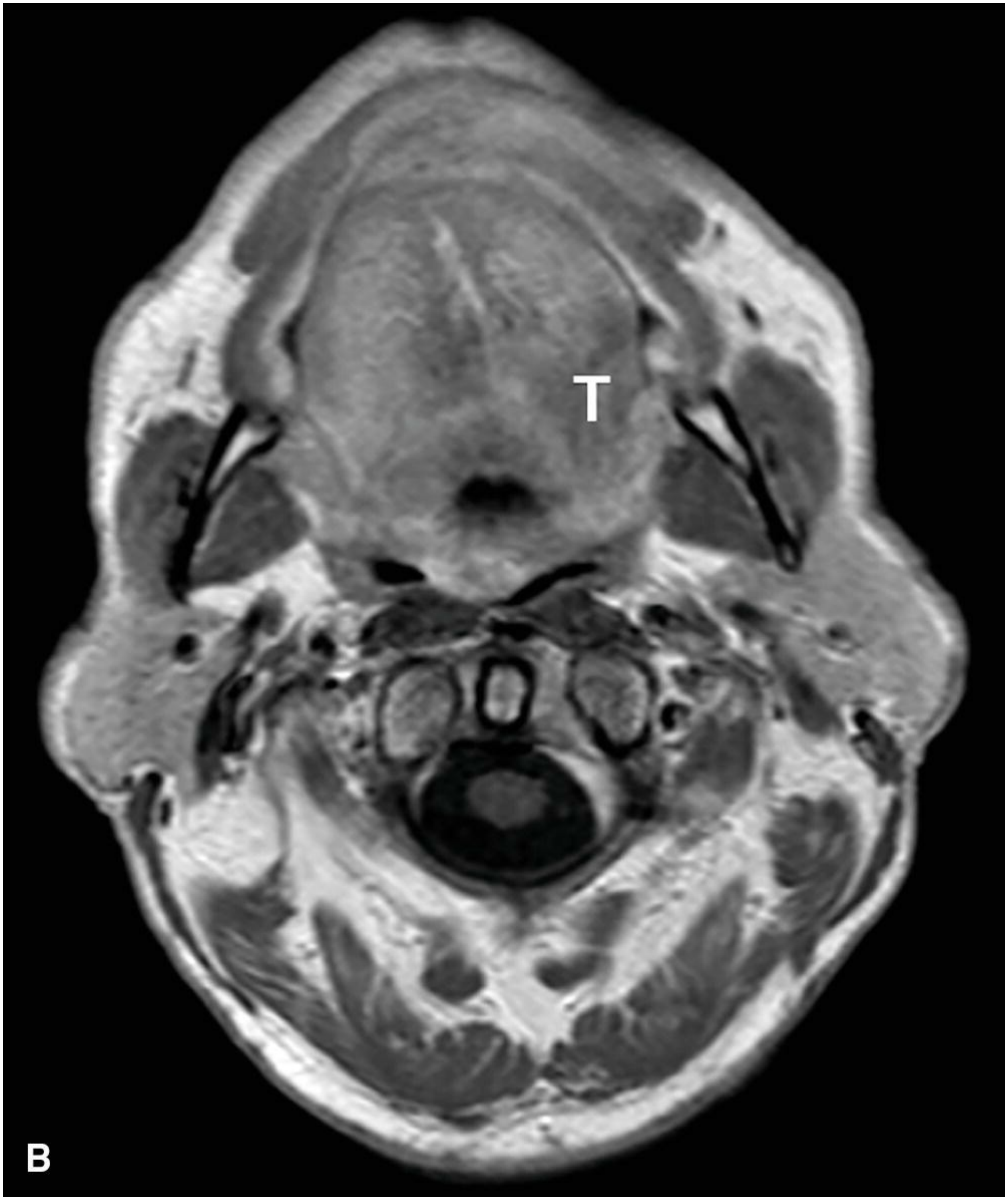
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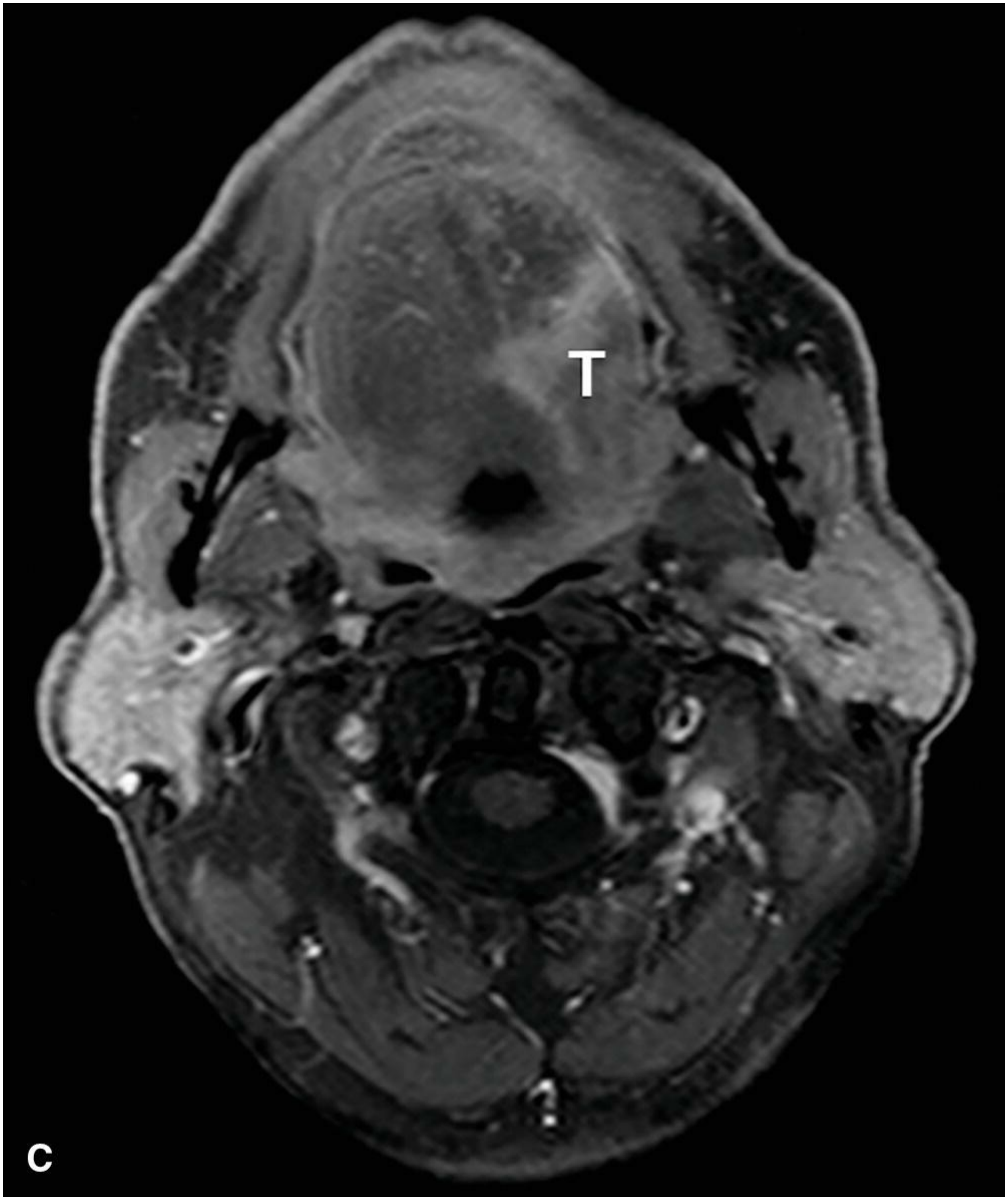
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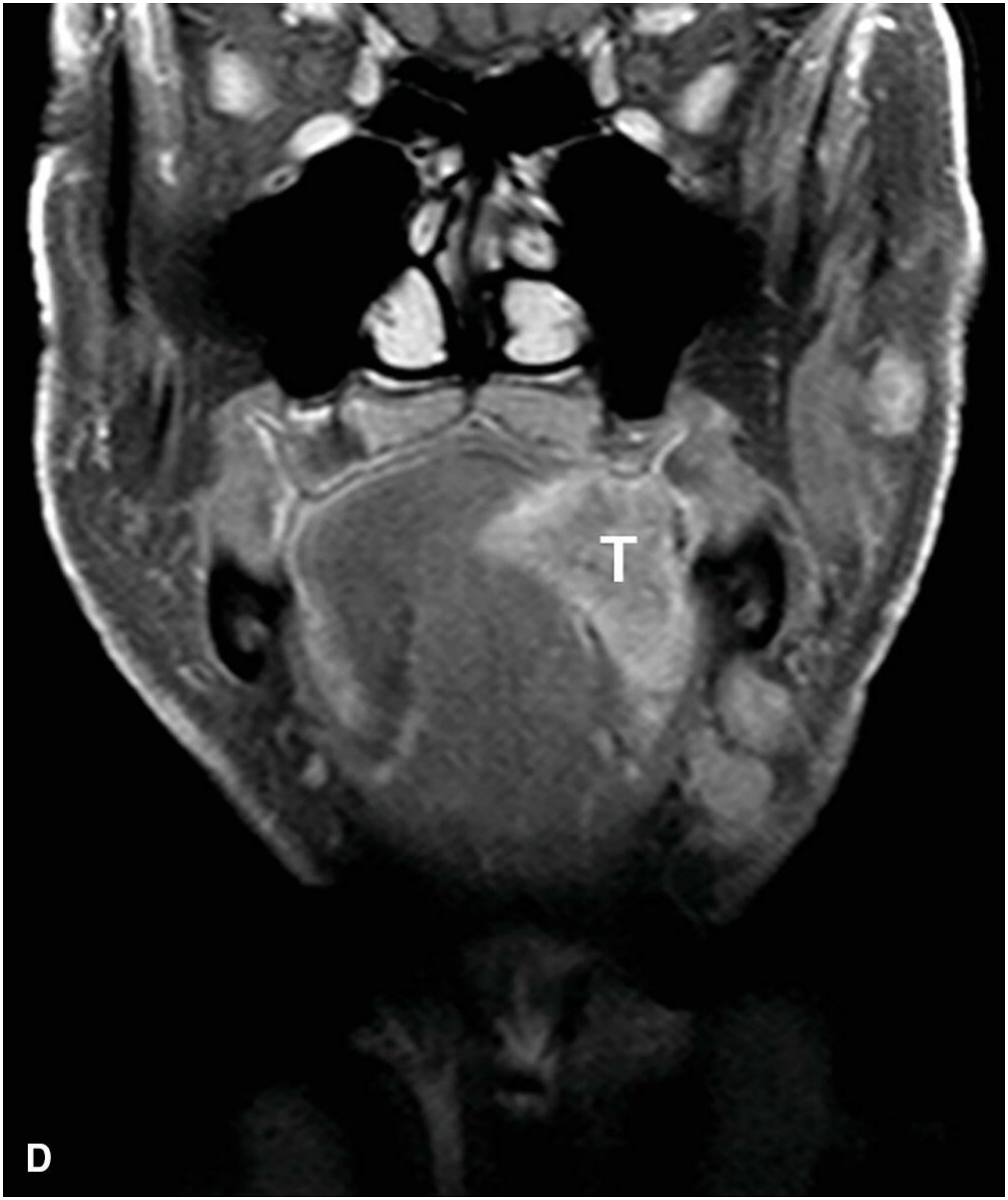
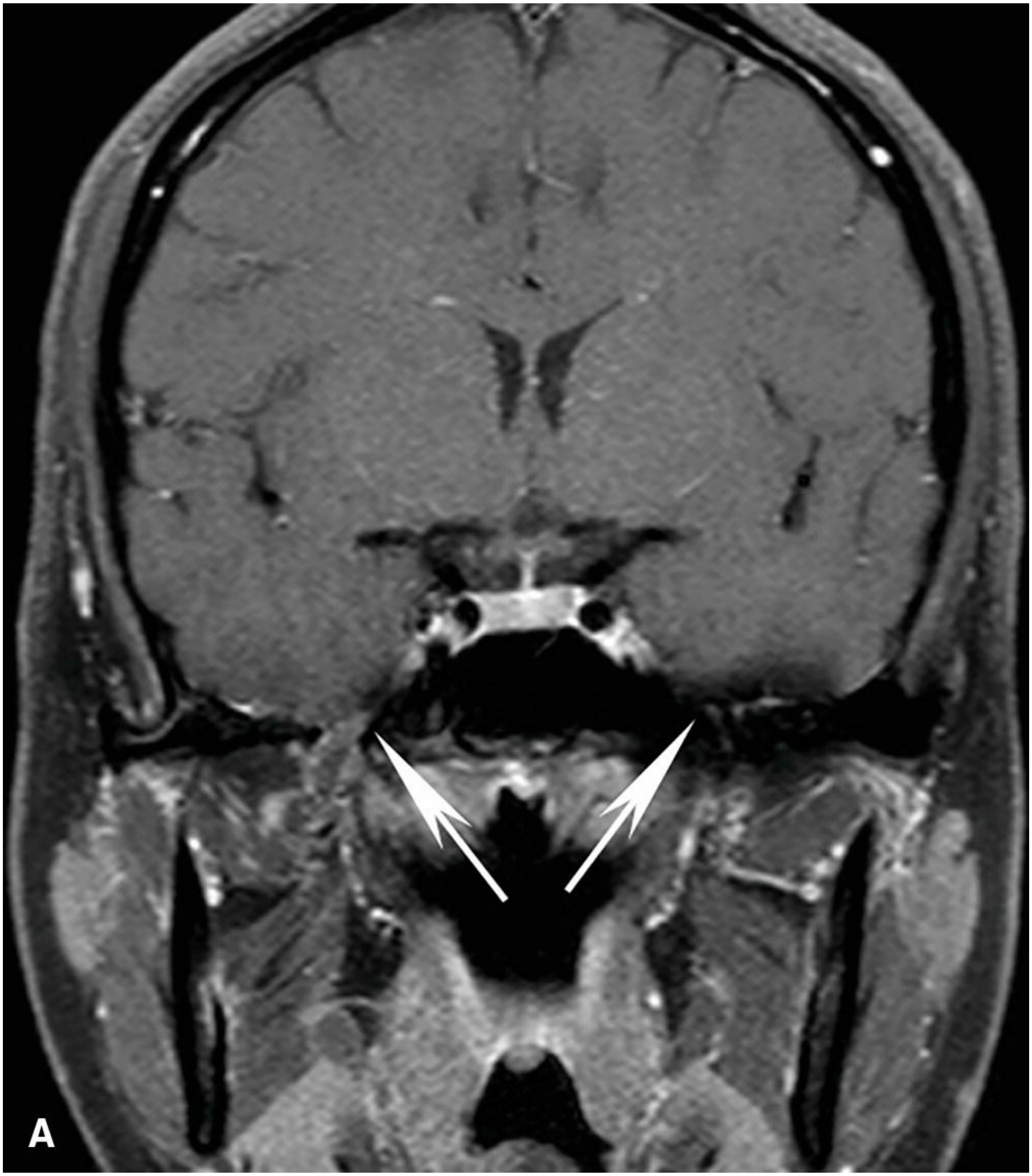


Figure 5.6. T1w and contrast-enhanced imaging for evaluation of cancer of the head and neck. Images are shown from a 59-year-old man with oral tongue squamous cell carcinoma. **A:** Axial T1w image without fat suppression. As discussed in the text, there is good depiction of normal anatomy. Muscle has intermediate signal (e.g., MS, *masseter*), and fat is very

bright (or hyperintense), for example, the subcutaneous fat (*black asterisk*). Cortical bone is dark, whereas the fatty marrow is bright (**A**, e.g., *white circle* around the right mandibular ramus). The tumor (T) has intermediate signal on the unenhanced T1w image and is not very conspicuous. Because this patient has a relatively fatty tongue, the tumor margins are still visible. **B:** Postcontrast axial T1w image without fat suppression. Because of the intrinsically bright signal associated with the fat in the tongue, this sequence does not show the enhancing tumor (T) well. Postcontrast axial **(C)** and coronal T1w image **(D)**, both with fat suppression. Note how the enhancing tumor (T) is much more conspicuous on the fat-suppressed images compared to the non–fat-suppressed image **(B)**.

Contrast-enhanced images are key for tumor evaluation and should be obtained in all head and neck MRIs unless contraindicated. Paramagnetic contrast agents have bright signal on T1w images, and therefore, T1w images are the main sequence used for evaluation of contrast enhancement. In order to better depict tissue enhancement, contrast-enhanced T1w images are obtained as fat-suppressed sequences (T1FS). On these sequences, the bright signal of fat is suppressed and the fat appears dark, accentuating the enhancement characteristics of normal tissues and tumors (Fig. 5.6). All head and neck MRIs should include contrast-enhanced T1FS images. However, it is noteworthy that fat-saturated images are more prone to artifacts, particularly at air–bone interfaces such as the skull base or at sites of metal implants, dental fillings, or dental implants (Table 5.2; Fig. 5.7). Therefore, at some institutions and for select applications, one or more sets of postcontrast T1w images without fat suppression may also be obtained, in addition to fat-suppressed images (Fig. 5.7). On non–fat-suppressed contrast-enhanced T1w images, tumor has a grayish hue, which is typically distinguishable from the brighter signal of fat although the enhancement is not as conspicuous as on T1FS images.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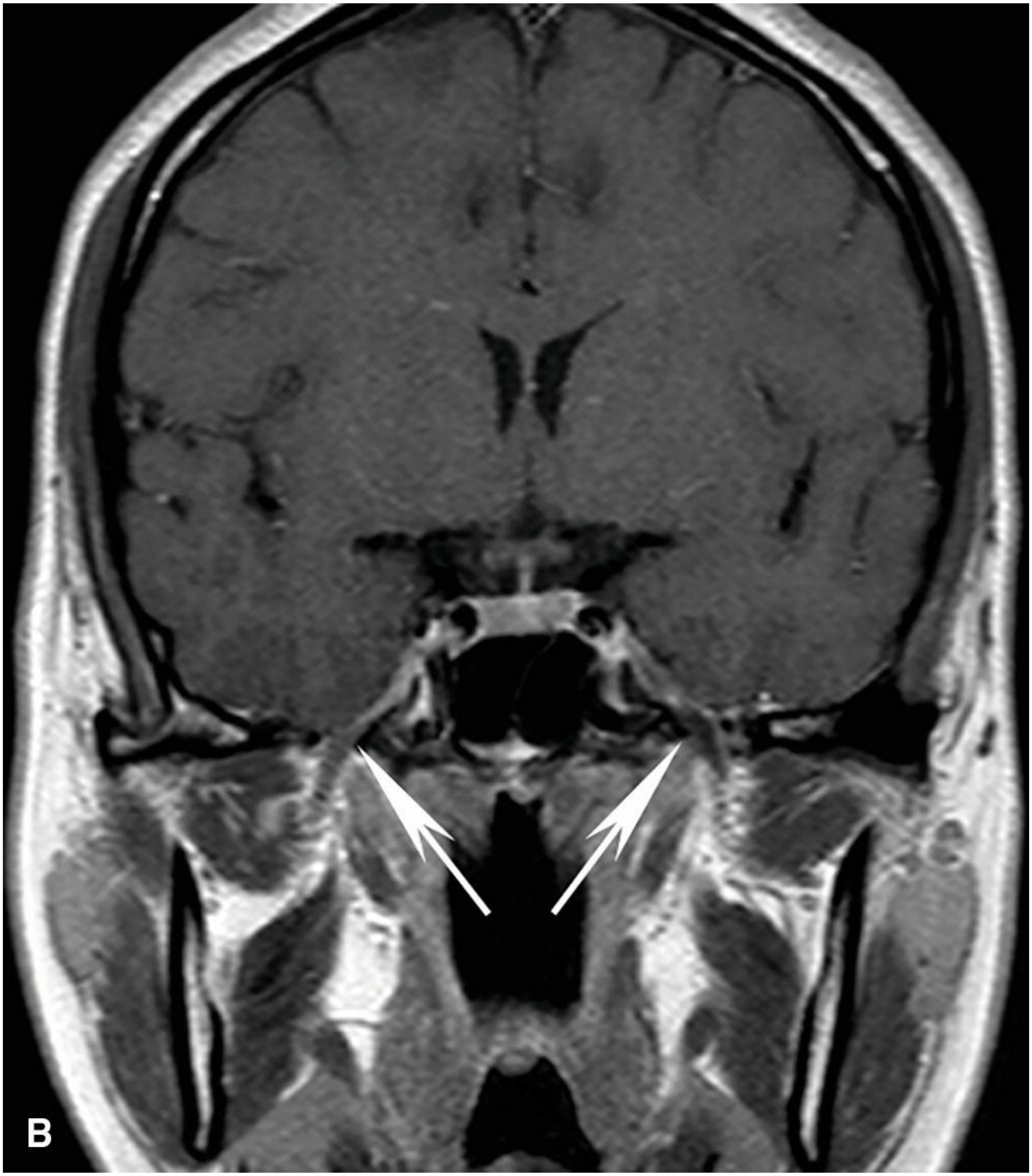
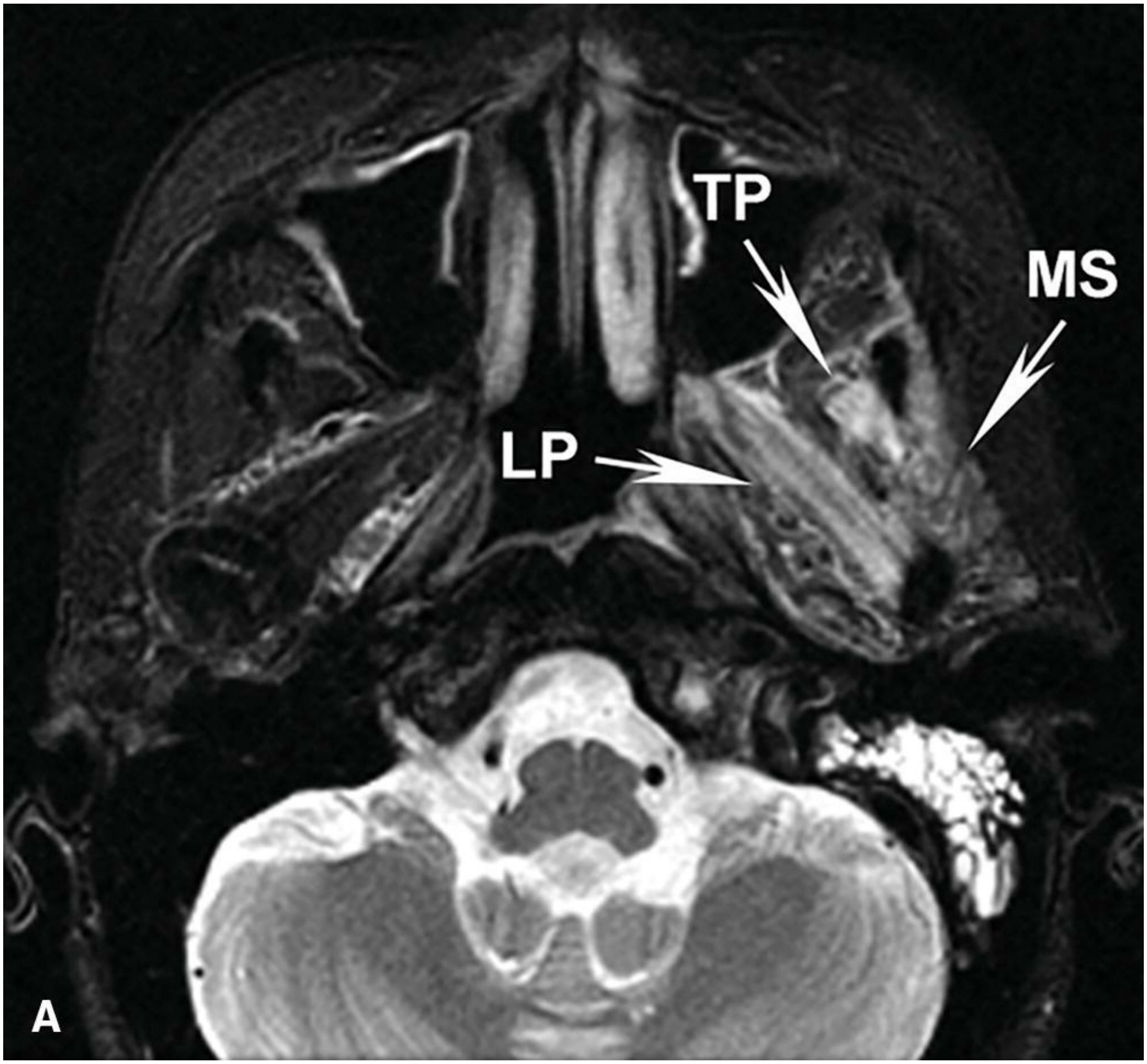


Figure 5.7. Effects of fat suppression on artifacts at the skull base. Coronal postcontrast T1w images with fat suppression **(A)** and without fat suppression **(B)** are shown. On the fat-suppressed image **(A)**, the foramen ovale (*arrows*) is partly obscured bilaterally, especially on the left side. On the other hand, the foramen ovale is well seen bilaterally on the T1w image obtained without fat suppression (**B**, *arrows*), and a normal intermediate

signal V3 branch is well seen on both sides. Therefore, although fat-suppressed T1w images are the primary sequence for evaluation of lesion enhancement, in select cases, addition of a non–fat-suppressed T1w sequence can improve diagnostic evaluation.

T2w and STIR Images.

T2w and/or STIR images are important sequences and are routinely obtained during head and neck imaging. On T2w images, fat is bright, although typically not as bright as T1 images, and muscle has intermediate to low signal (Table 5.2). Unlike T1 images, fluid is very bright on T2w images. On T2w images, tumor typically has intermediate signal, but this can vary from hypointense to hyperintense relative to muscle depending on the specific tumor type and tumor cellularity. This sequence typically provides good contrast between tumor and muscle. Tumor-associated edema also has high signal, typically higher than the signal of cellular tumor itself, which needs to be taken into account when evaluating invasion of anatomic structures such as marrow, when distinction between reactive edema and tumor invasion is important. Tumors with high cellularity tend to have relatively lower signal on T2w images compared to less cellular and more loosely packed tumors. As would be expected, the necrotic part of a tumor would have higher signal approaching that of fluid, and T2w images are a good sequence for identification of nodal inhomogeneity or necrosis, confirmed by demonstration of lack of internal enhancement on postcontrast T1w images (necrotic tumor components do not enhance). T2w images can also be obtained with fat suppression, to subdue the bright signal of fat and accentuate relatively hyperintense tumor and edema (Fig. 5.8). Fat-suppressed T2w images and STIR images (discussed next) are especially important for the evaluation of skull base and nasopharynx and are also very useful for demonstrating edema associated with denervation changes (Fig. 5.8).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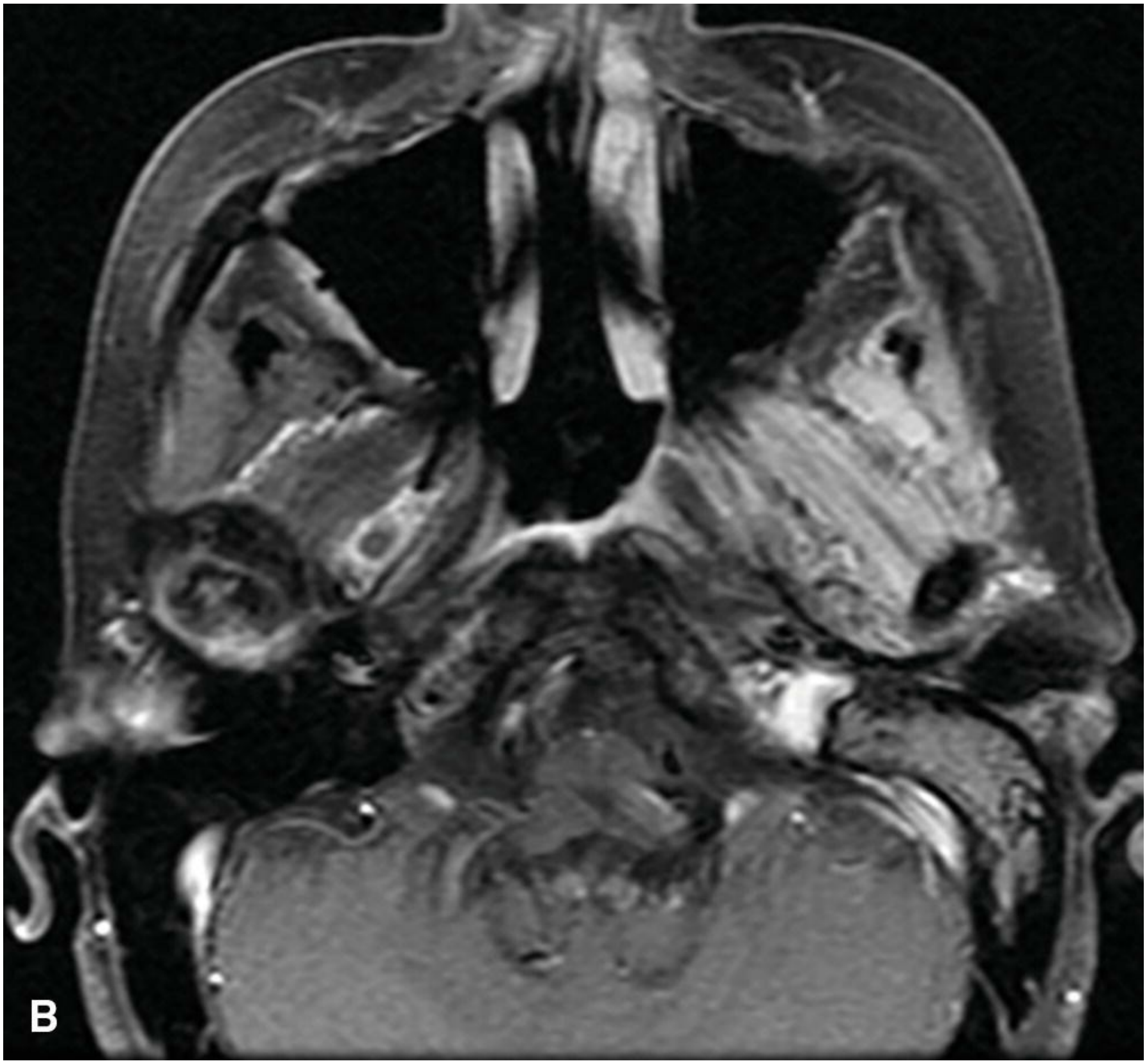


Figure 5.8. Denervation changes on MRI and utility of fat-suppressed T2w images. Axial fat-suppressed T2w **(A)** and contrast enhanced T1w **(B)** images are shown from a 43-year-old woman with recurrent nasopharyngeal cancer to the left Meckel cave (not shown). There are typical denervation changes in the distribution of the mandibular division of the left trigeminal nerve (V3) with hyperintense T2 signal **(A)** and abnormal enhancement **(B)** in the lateral pterygoid (LP), temporalis (TP), and masseter (MS) muscles. Note the preservation of muscle architecture with striations that is typical of denervation change and should not be mistaken for tumor. Fat-suppressed T2w images (or STIR images—not shown) are excellent for demonstrating edema.

Although technically different, the signal characteristics of tissues on STIR images (Fig. 5.9) are in many ways similar to, and follow what is seen on, fat-suppressed T2w images. Although the signal to noise of a typical STIR image is lower than that of T2w images, this is made up for by the increased soft tissue contrast. STIR has very good soft tissue contrast, has more uniform suppression of fat signal, and is excellent for demonstrating high signal from soft tissue tumors or edema[9,10] (Fig. 5.9; Table 5.2). Similar to fat-saturated T2w images, fat is dark on STIR images. Simple fluid and edema are even brighter on STIR than T2w images, and these sequences are excellent for demonstrating edema or necrosis within the tumor or pathologic lymph nodes. Tumor also tends to be brighter on STIR compared to T2w images. It is noteworthy that normal mucosal surfaces may have high signal intensity on STIR images, and this should not be mistaken for pathology.[11] All head and neck MRIs should include at least one set of fat-suppressed T2w or STIR images. Please refer to Table 5.2 for a more detailed description of tissue signal on different MRI sequences.

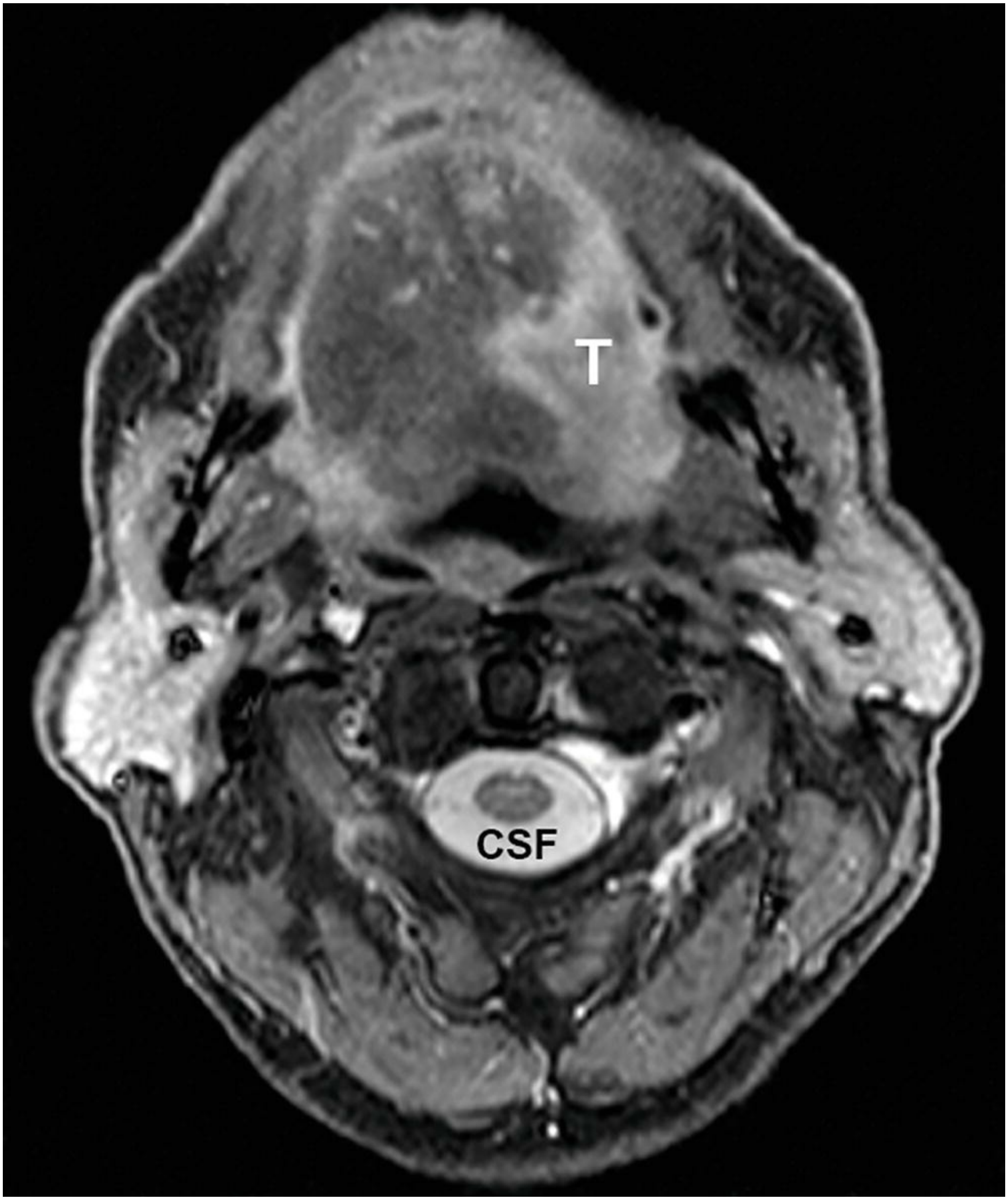


Figure 5.9. Tumor appearance on STIR images. STIR image is shown from the same case displayed in Figure 5.6. Note the bright signal of the tongue cancer (T) compared to adjacent tissues. Fluid, such as that of cerebrospinal fluid (CSF), is very bright on STIR.

Comparative Overview of Strengths and Weaknesses of CT Technique for Head and Neck Cancer Imaging

Some of the advantages of CT and MRI were discussed in the preceding sections, and the techniques are also compared in greater detail in Table 5.3. Briefly, advantages of CT accounting for its popularity include rapid image acquisition, widespread availability, and relatively lower cost compared to MRI. On the typical modern CT scanner with 64 or more slices, a neck CT is obtained in <10 seconds. As a result, CT is generally better tolerated by patients compared to MRI where the typical scan times will be 20 to 30 minutes or even more in specialized applications. Imaging of the head and neck, particularly below the level of the hard palate, is prone to motion artifact that may result from swallowing or other motion if the patient cannot remain still. The problem is further exacerbated in patients having difficulty breathing or difficulty clearing secretions. Therefore, from a diagnostic image quality perspective, the short scan times of CT represent a considerable advantage over MRI for cancers below the level of the hard palate. CT is also a safer environment for the evaluation of acutely ill patients or patients with respiratory difficulties who would have difficulty lying still in the supine position for a prolonged period of time.

Table 5.3 Comparison of Relative Strengths of CT and MRI for Head and Neck Cancer Imaging

	CT	MRI
Diagnostic and image quality, artifact	■ Less prone to motion degradation and swallowing artifact, particularly below the level of the hard palate ■ Complementary to MRI for evaluation of bone, better visualization of bone architecture, and early cortical invasion ■ Single plane acquisition disadvantage for certain areas such as palate but at least in part offset by the ability to generate high-quality reformats in sagittal and coronal planes on modern scanners	■ Higher soft tissue contrast ■ Typically less prone to dental implant and metallic hardware-related artifact ■ Prone to artifact at interfaces between soft tissues or bone and air ■ Complementary to CT for evaluation of bones, better visualization of marrow edema, and marrow invasion ■ Multiplanar acquisition
Patient tolerance, safety, and exposure to ionizing radiation	■ Rapid acquisition (actual scan time within seconds) is better tolerated by patients, particularly patients who are ill and patients with respiratory problems or difficulty clearing secretions who may have a hard time remaining motionless for a prolonged period of time ■ Higher likelihood of occurrence and severity of anaphylactoid and anaphylactic reactions compared to MRI contrast agents ■ Exposure to ionizing radiation	■ No exposure to ionizing radiation although practically this is not a significant or determining factor in the typical adult head and neck cancer population ■ Risk of rare but potentially fatal adverse reaction of nephrogenic systemic fibrosis in patients with significantly impaired renal function
Accessibility and cost	■ Generally more accessible ■ Costs less than MRI	■ Less accessible, especially outside large centers ■ Typically costs more than CT

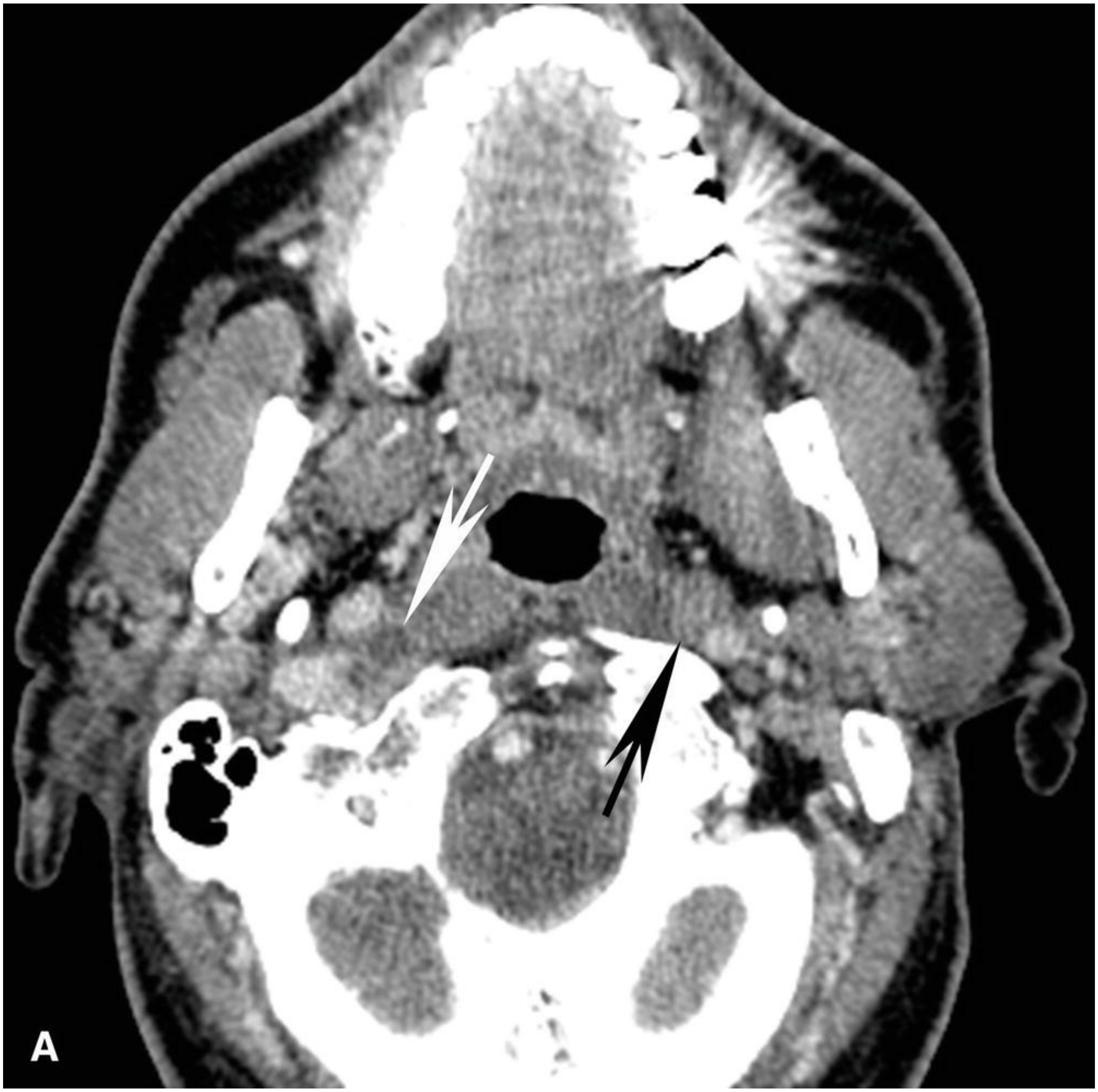
MRI is frequently used as an adjunctive tool for better delineation of lesions not clearly seen on CT and for specialized applications such as evaluation of PNS of tumor or intracranial extension. There is also typically less dental artifact on MRI compared to CT, although this is not always predictable. CT and MRI are generally considered complementary for the evaluation of bone invasion. CT is superior for detection of cortical erosion (Fig. 5.4), whereas MRI is superior for determination of marrow invasion, such as infiltration by nasopharyngeal cancer. Additional site-specific advantages of each modality are discussed later in this chapter. There is greater risk of adverse reactions such as anaphylactic reactions with iodinated contrast agents used for CT compared to MRI contrast agents. There is also a risk of impaired renal function with CT contrast agents, mainly in patients with preexisting renal failure. However, although MRI contrast agents do not induce renal failure, there is a rare but potentially fatal complication of nephrogenic systemic fibrosis associated with gadolinium-based MRI contrast agents in patients with severely impaired renal function,[12] and an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 is generally considered an absolute contraindication to administration of gadolinium. MRI is also contraindicated in patients with certain metallic implants, accidental foreign bodies, and most patients with pacemakers, although newer pacemakers with conditional MRI compatibility are increasingly becoming available and may no longer represent an absolute contraindication in the future. A more detailed discussion of potential adverse reactions and safety is beyond the scope of this chapter. A summary comparison of strengths and relative disadvantages of CT and MRI is provided in Table 5.3.

Molecular Functional Imaging: Positron Emission Tomography in Head and Neck Cancer

Overview of PET Principles and Acquisition

PET has emerged as an essential adjunctive modality for evaluation of head and neck cancer.[13,14] PET is a functional technique that evaluates cellular metabolism. This is achieved by “tagging” metabolites of interest with specific radiopharmaceuticals, which in turn can be detected and localized with a PET scanner. When integrated with an anatomic technique like CT,

this provides a robust functional evaluation while enabling accurate anatomic localization, which is very important given the complex anatomy in the head and neck. Therefore, current standard practice is to perform a combined PET/CT for evaluation of head and neck cancer.[13,14] Most PET/CTs for head and neck cancer are performed using the radiopharmaceutical 2-18F-fluoro-2-deoxy-D-glucose (FDG), a glucose analog that is taken up by cells but is not metabolized.[13,14] The rationale for FDG–PET cancer imaging is that in general, cancer cells have greater uptake on PET than do normal tissues (known as Warburg effect) (Fig. 5.10). However, one must take into account that increased FDG uptake is not specific to cancer cells and may be seen in context of inflammation/infection including biopsy sites, some benign neoplasms, or increased muscular activity under certain circumstances. This needs to be taken into account when interpreting PET scans; to be discussed later.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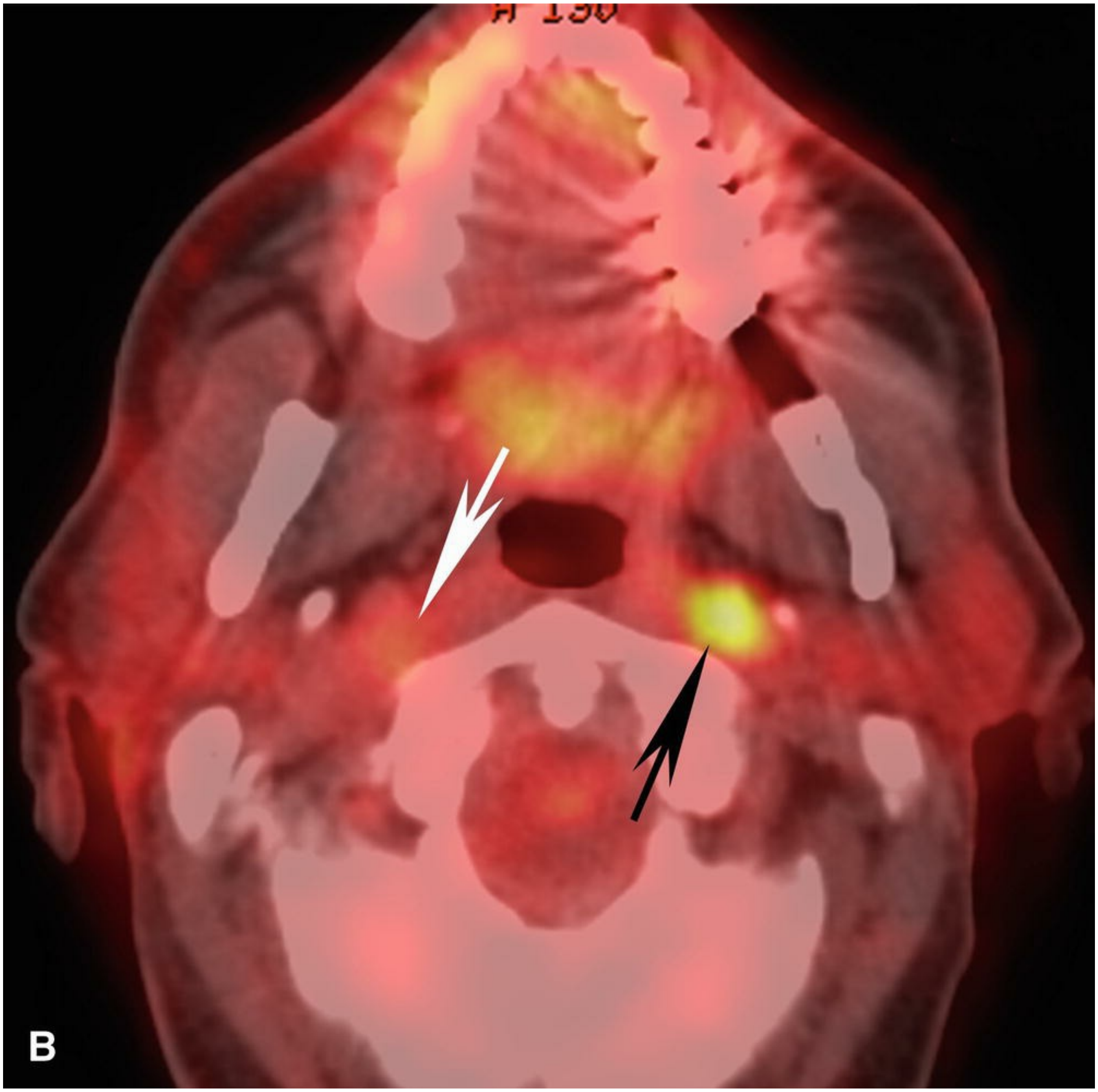


Figure 5.10. Advantages and pitfalls of PET for detection of metastatic lymph nodes. Axial contrast-enhanced CT scan **(A)** and fused PET image **(B)** are shown from a 60-year-old man with squamous cell carcinoma of the left lateral pharyngeal wall (not shown). There is abnormal, markedly increased uptake in the left lateral retropharyngeal lymph node (*black arrow*) that on the CT is barely visible and cannot be convincingly characterized as abnormal but which is quite evident on the PET study. This illustrates the increased sensitivity of PET compared to CT. On the other hand, there is a subtle but clearly necrotic, pathologic right lateral retropharyngeal lymph node seen on CT without significant uptake on PET (*white arrow*). Necrotic

nodes are a known potential pitfall of PET because there may be insufficient metabolically active tissue to permit visual detection. This case highlights the importance of combined interpretation of a diagnostic CT and PET scan.

Currently, the CT portion of a PET/CT can be performed using two techniques. In one approach, a low-dose CT is obtained without IV contrast. This provides adequate anatomic localization, but the CT portion is otherwise not considered a diagnostic study. When this is done, the standard practice would be to interpret the PET/CT scan in conjunction with a dedicated contrast-enhanced CT obtained in a separate session. It is important to interpret these scans in conjunction with a dedicated contrast-enhanced neck CT because the contrast-enhanced CT provides superior anatomic information for tumor delineation and invasion of critical structures, including vessels.[13,15] This is the approach used at our institutions, although in practice, the two exams may end up temporally separated. The contrast-enhanced study is also important for identification of necrotic lymph nodes, which may not demonstrate significant uptake on the PET scan (Fig. 5.10). The other approach is to perform combined PET/CT scanning with a diagnostic quality contrast-enhanced CT. The advantage of this approach is that both tests are obtained in a single session. However, the use of CT contrast media in PET/CT has the potential to introduce artifacts and may result in an overestimation of PET attenuation factors. The clinical significance of this is unclear at this time with some authors suggesting that the effect is not clinically significant whereas others suggesting that interpretation can be adversely affected.[15–18] There are in addition other limitations to this approach such as an excessively large CT field of view, and inability to angle the gantry so as to avoid artifact from dental fillings.

PET/CT Interpretation

The FDG uptake by a tumor is typically displayed with a color overlay map to demonstrate metabolic activity (Figs. 5.10 to 5.13). The overlay map can also be fused with the CT part of the exam for display for easier anatomic colocalization (Figs. 5.10 to 5.13). The uptake on PET can also be evaluated semiquantitatively using the standard uptake value (SUV), a measure of the radioactivity within a region of interest (e.g., tumor) corrected for the amount of radioactivity injected and the patient’s body weight. The SUV by itself is

not specific, and a number of benign processes can result in false-positive uptake on a PET scan, as discussed below. Nonetheless, SUV is a useful indicator of the potential of a lesion to represent a malignancy.[13]

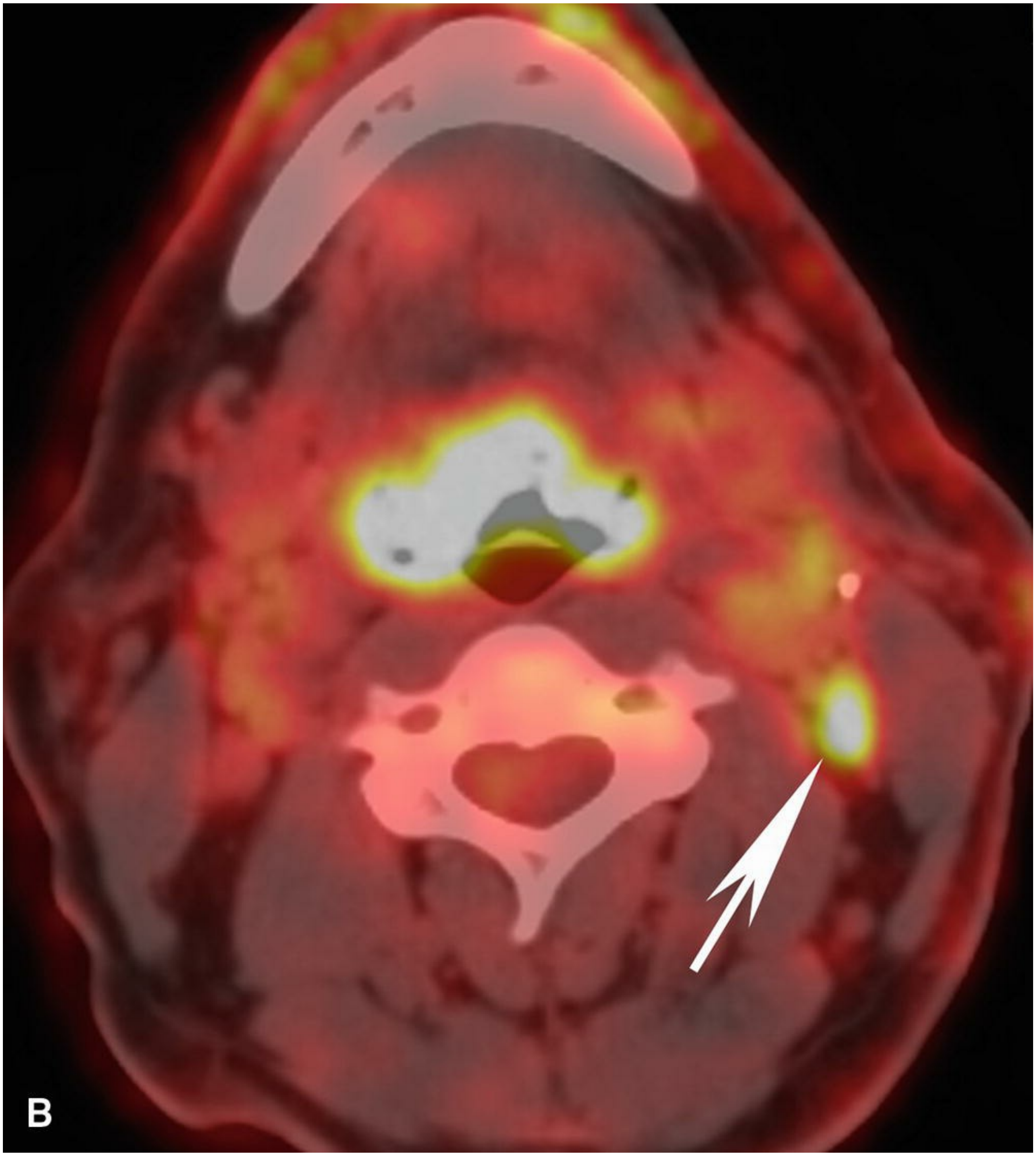
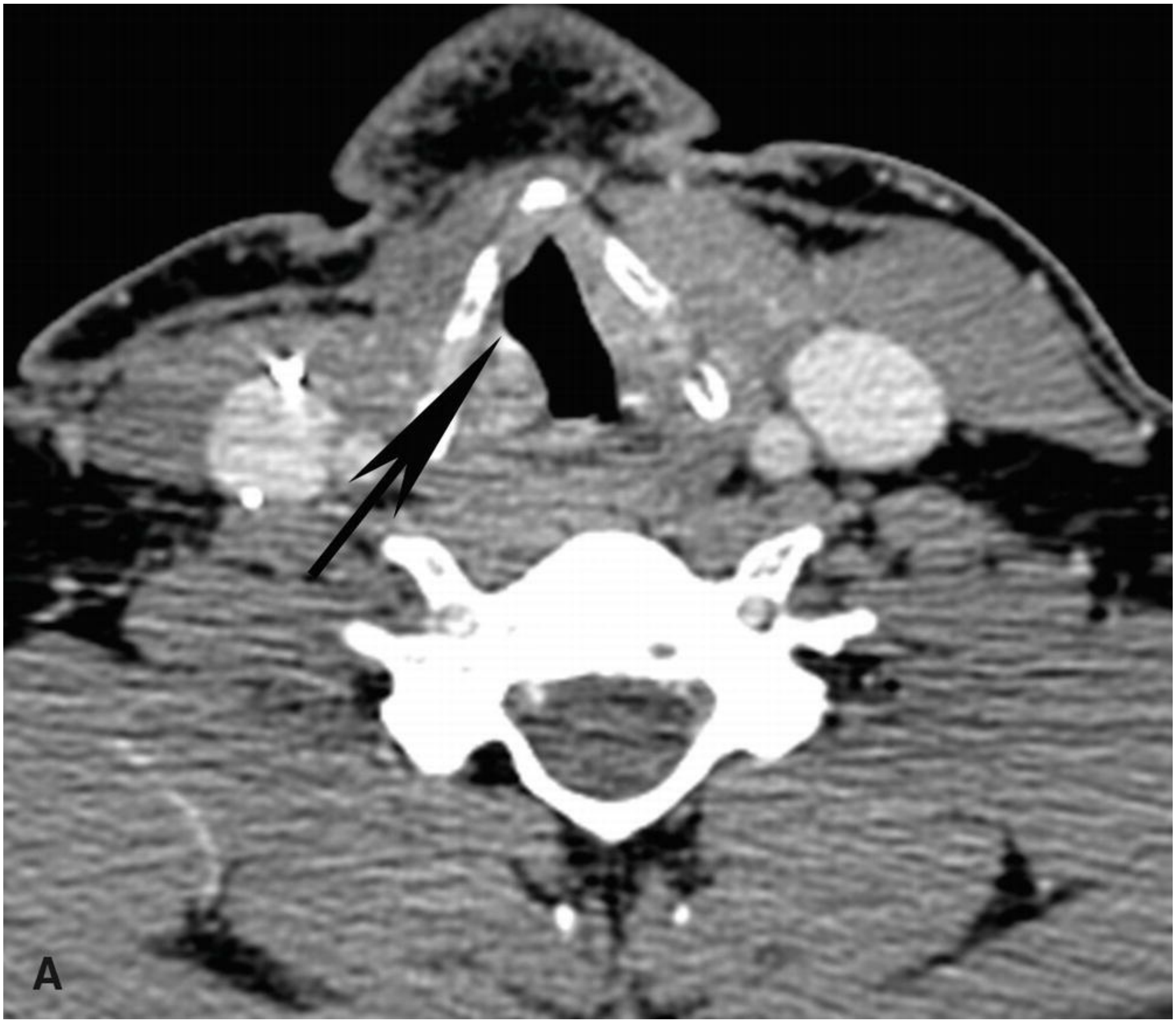


Figure 5.11. Pitfalls and false positives in PET: lymphoid tissues of the Waldeyer ring. Axial contrast-enhanced CT scan **(A)** and fused PET image **(B)** are shown from a 50-year-old with carcinoma of unknown primary who presented with an N2C neck. On CT, there are enlarged lingual tonsils at the base of the tongue without a focal enhancing mass. On PET, there is diffusely increased uptake of this lymphoid tissue. However, all base of tongue biopsies were negative. Note the pathologic level IIb node detected on PET

(*arrow*). On CT, the node is prominent but cannot be characterized as abnormal by anatomic imaging criteria.

Figure 5.12. Pitfalls and false positives in PET: lymphoid tissues of the Waldeyer ring. Axial contrast-enhanced CT scan **(A)** and fused PET image **(B)** are shown from a 52-year-old with biopsy-proven squamous cell carcinoma of the right base of the tongue. Similar to the case in Figure 5.11, there is diffuse uptake at the base of the tongue without clear focally increased uptake at the site of tumor on the right (*long arrow*). On CT, there is asymmetric enlargement of the right base of tongue tissues (*long arrow*). Although by itself this is insufficient for a confident diagnosis, it is useful for directing the biopsy, which demonstrated cancer at that site. Note the large,

partly necrotic, right level II pathologic nodal mass with diffusely increased uptake on PET (*short arrows*).



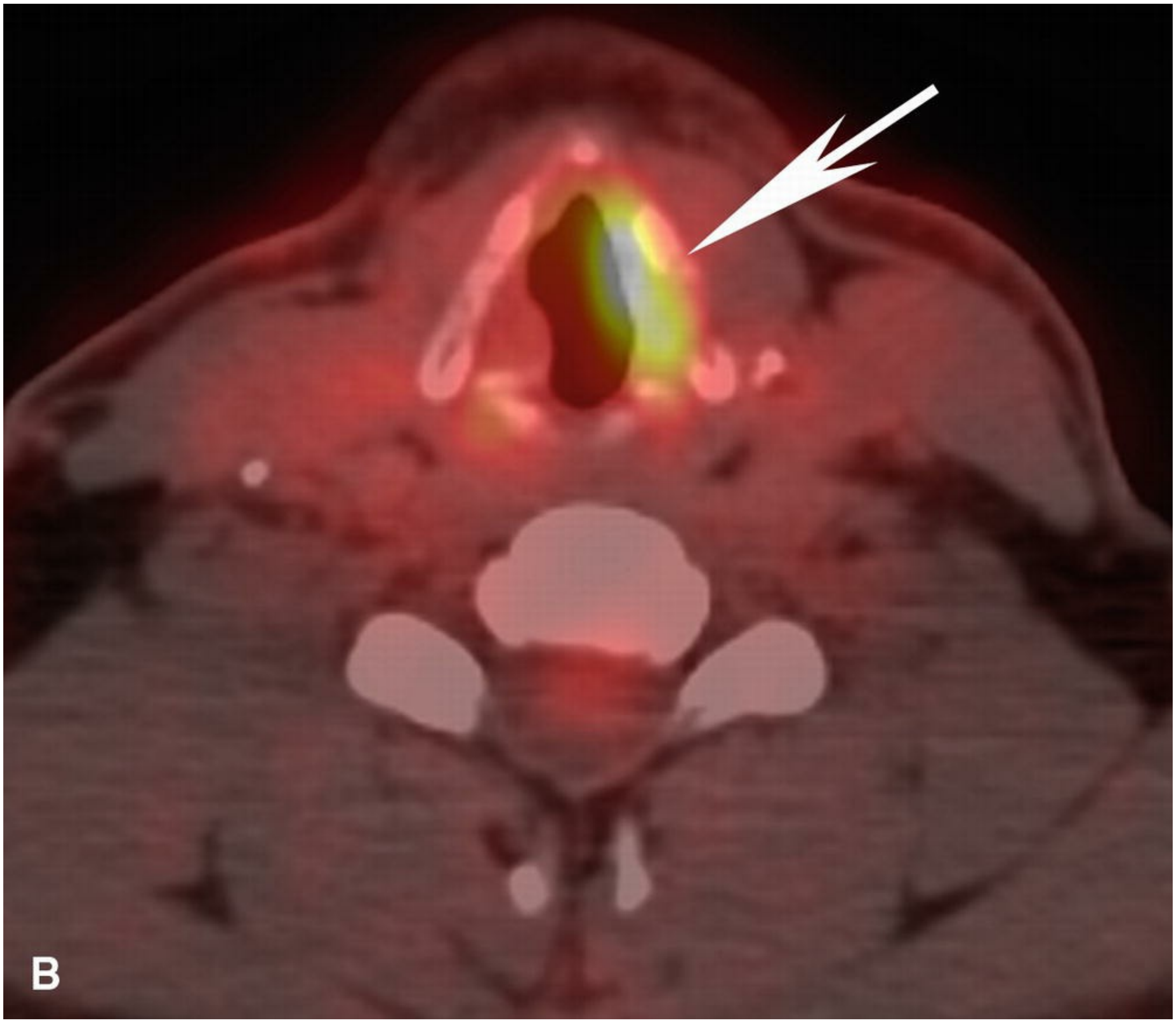


Figure 5.13. Pitfalls and false positives in PET: asymmetric muscle uptake associated with vocal cord paralysis. Axial contrast-enhanced CT scan **(A)** and fused PET image **(B)** are shown from a 33-year-old patient operated for thyroid cancer with right vocal cord paralysis. The CT image demonstrates a patulous laryngeal ventricle on the right (*black arrow*) typical of vocal cord paralysis. The PET image demonstrates typical compensatory increased activity in the normal left true vocal cord (*white arrow*). This should not be mistaken for tumor.

The most common SUV used as a threshold between a benign and potentially malignant lesion is 2.5. This value has been extrapolated from a study of pulmonary lesions performed in 1993[19] and has been used by some for evaluation of head and neck cancer.[20] Therefore, although it is useful as a

reference for potential pathology, there is no clear evidence that this threshold can be extrapolated to lymph nodes or tissues and lesions outside the thorax. For example, others have used an SUV of 3.5 to 4 as threshold for evaluation of lymphadenopathy,[21] and one study showed that the greatest specificity for determination of metastatic nodal disease in squamous cell carcinoma (SCC) was achieved when a threshold of 5 was used.[22] As discussed by Escott,[13] another pitfall of using strict SUV criteria for determination of lymphadenopathy is that small pathologic lymph nodes may have an SUV value below an accepted threshold and thus be visually difficult to call abnormal. This highlights the importance of using the SUV as a guide, rather than absolute determining value, and carefully correlating with findings on the contrast-enhanced CT for determination of pathologic lesions and lymphadenopathy.

Pitfalls, Artifacts, and False Positives in PET Imaging

It is also important to be aware of general pitfalls, potential false positives, and artifacts during PET/CT interpretation. An exhaustive list of false-positive and false-negative findings is beyond the scope of this chapter, but increased FDG uptake can be seen in a variety of nonneoplastic pathologies such as inflammatory and infectious processes, including that seen after radiation therapy, as well as uptake from normal anatomic structures such as muscle, brown fat, salivary glands, and lymphoid tissue, particularly the tissues of Waldeyer ring[13,23] (Figs. 5.11 and 5.12). Asymmetric uptake can occur with vocal cord paralysis (Fig. 5.13) or after surgery or other posttreatment changes resulting in asymmetric muscle uptake. A number of benign lesions can also result in increased FDG uptake including thyroid adenomas, Paget disease, and fibrous dysplasia. Thyroiditis and Graves disease can also result in increased FDG uptake. One must also be aware of different artifacts including those secondary to metallic implants or dense IV or enteric contrast falsely appearing as hypermetabolic areas.

EVALUATION OF TUMORS—GENERAL CONSIDERATIONS

Overview

Although there are important differences in tumor behavior, spread pattern, and consequently imaging evaluation according to the primary site, the general approach to interpreting head and neck cancer studies is similar regardless of specific tumor or primary location. A careful, systematic evaluation is essential for optimal imaging assessment and should parallel the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system.[24] Using this approach, the report will follow a logical and clinically relevant structure for optimal communication of results. In this regard, it is not absolutely necessary to provide the specific radiologic tumor stage in the report, the pros and cons of which are beyond the scope of this chapter. What is important is to evaluate and identify involvement of critical structures that would alter tumor stage and consequently patient management.

As discussed earlier, one role of imaging is to evaluate a lesion's characteristics, provide a differential diagnosis, and when necessary help with biopsy planning. Imaging can also be helpful in clinically misleading presentations, and sometimes the radiologist is the first to suggest the presence and site of a head and neck cancer (Fig. 5.14). However, frequently, at the time of initial evaluation, the diagnosis has already been made, and the main role of imaging is to stage the tumor. The added value of imaging in that scenario is typically to upstage the clinical assessment by identifying involvement of critical structures, lymph nodes, or distant metastases that are not reliably identified clinically. Imaging can also guide biopsy when there are potentially important equivocal findings. Furthermore, imaging plays a key role in follow-up and surveillance of cancers to evaluate response to treatment, progression of disease, and tumor recurrence.

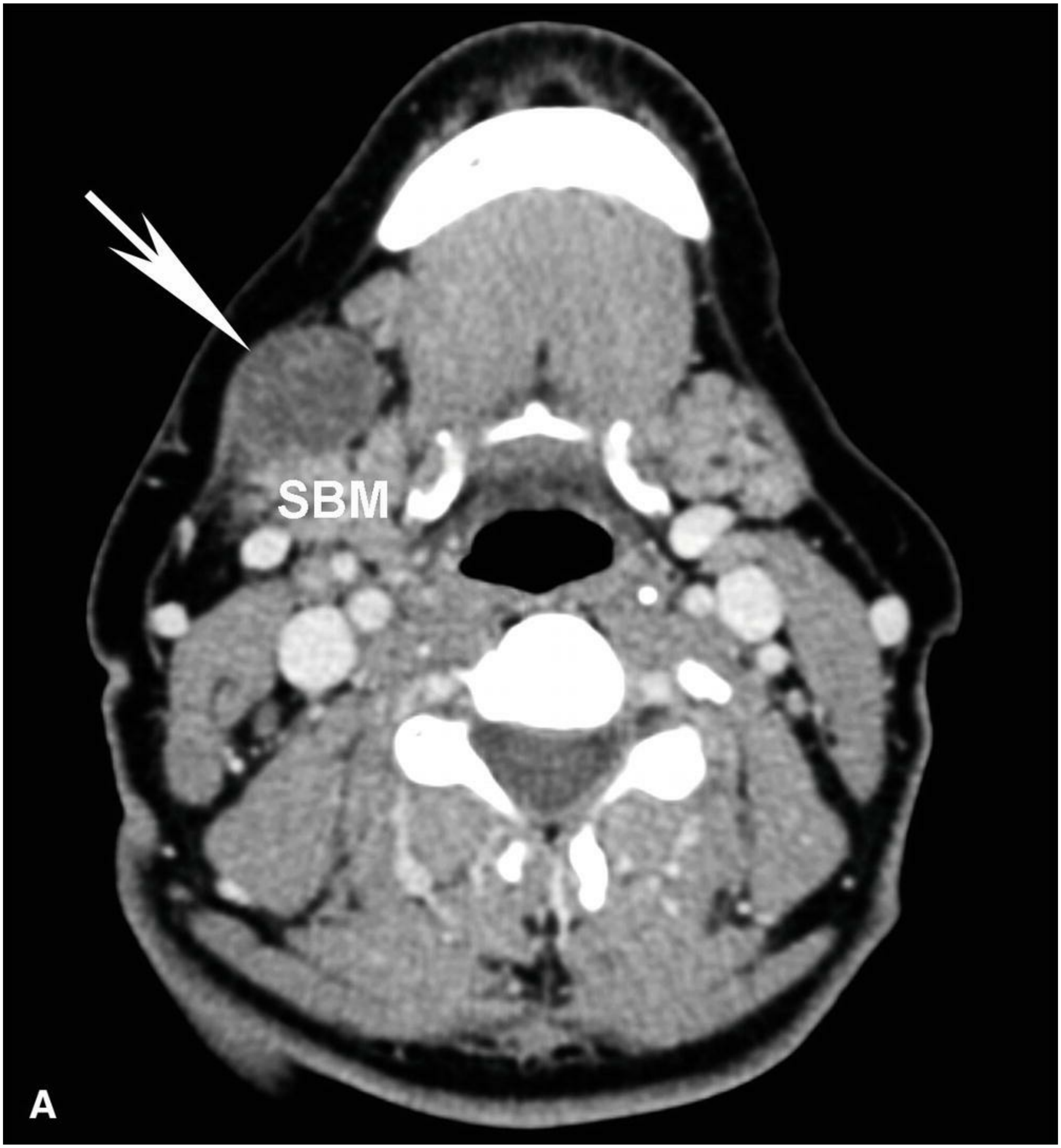

SBM
A

Figure 5.14. Nodal metastasis from squamous cell carcinoma presenting clinically as a submandibular region mass. Axial contrast-enhanced CT images in a patient referred for evaluation of a new right submandibular mass demonstrate an inhomogeneous enlarged level IB node (*large arrow*; **A**) anterior to the submandibular gland (SBM), compressing and displacing the gland posteriorly. Images more superiorly demonstrate a small buccal mucosal primary cancer (*small arrows*; **B**). The *small black arrows* mark the medial margin of the tumor. The *small white arrow* marks the lateral margin

of the tumor, resulting in partial obliteration and asymmetry of adjacent buccal space fat. Evaluation of subtle loss of symmetry is very useful for detection of small lesions in the neck.

Tumors can spread by direct extension with encroachment and invasion of nearby structures, lymphatic dissemination, and hematogenous dissemination to distant sites, as reflected in the TNM staging.[24] A less common but important route of spread for head and neck cancer is along the nerve bundles, referred to as PNS of tumor.[25,26] In addition, head and neck cancer patients are also at risk for the presence of a second primary cancer, which can arise from the upper aerodigestive tract, the lungs, or less frequently other organs.[27–32] A thorough evaluation will lead to proper staging at the time of diagnosis and, in turn, will help determine the appropriate treatment regimen.[24] The following sections will provide an overview of imaging characteristics and approach to evaluation of head and neck cancer.

Approach to Evaluation and General Characteristics of Head and Neck Cancer on CT, MRI, and PET

The majority of head and neck cancers are SCCs. Although it is not always possible to distinguish different malignancies based on imaging alone, SCCs, especially when large, tend to have a more invasive or aggressive appearance with irregular enhancing margins, invasion rather than displacement of adjacent normal anatomic structures, and areas of internal heterogeneity/necrosis or ulceration (Figs. 5.3, 5.4, and 5.6). More indolent or benign neoplasms such as benign salivary gland tumors tend to have more homogenous appearance with smooth rounded margins, however, biopsy is typically required for definitive diagnosis. Malignant salivary gland neoplasms may have a similar appearance as SCC on imaging and require biopsy for diagnosis (Fig. 5.15). For necrotic or cystic lesions, nodularity and irregularity of the margins of the lesion favors a malignant process over benign cystic lesions or abscesses,[8] but there can be overlap in appearance, and without clinical information or biopsy, the imaging appearance may not be sufficient for a definitive distinction from inflammatory or infectious lesions.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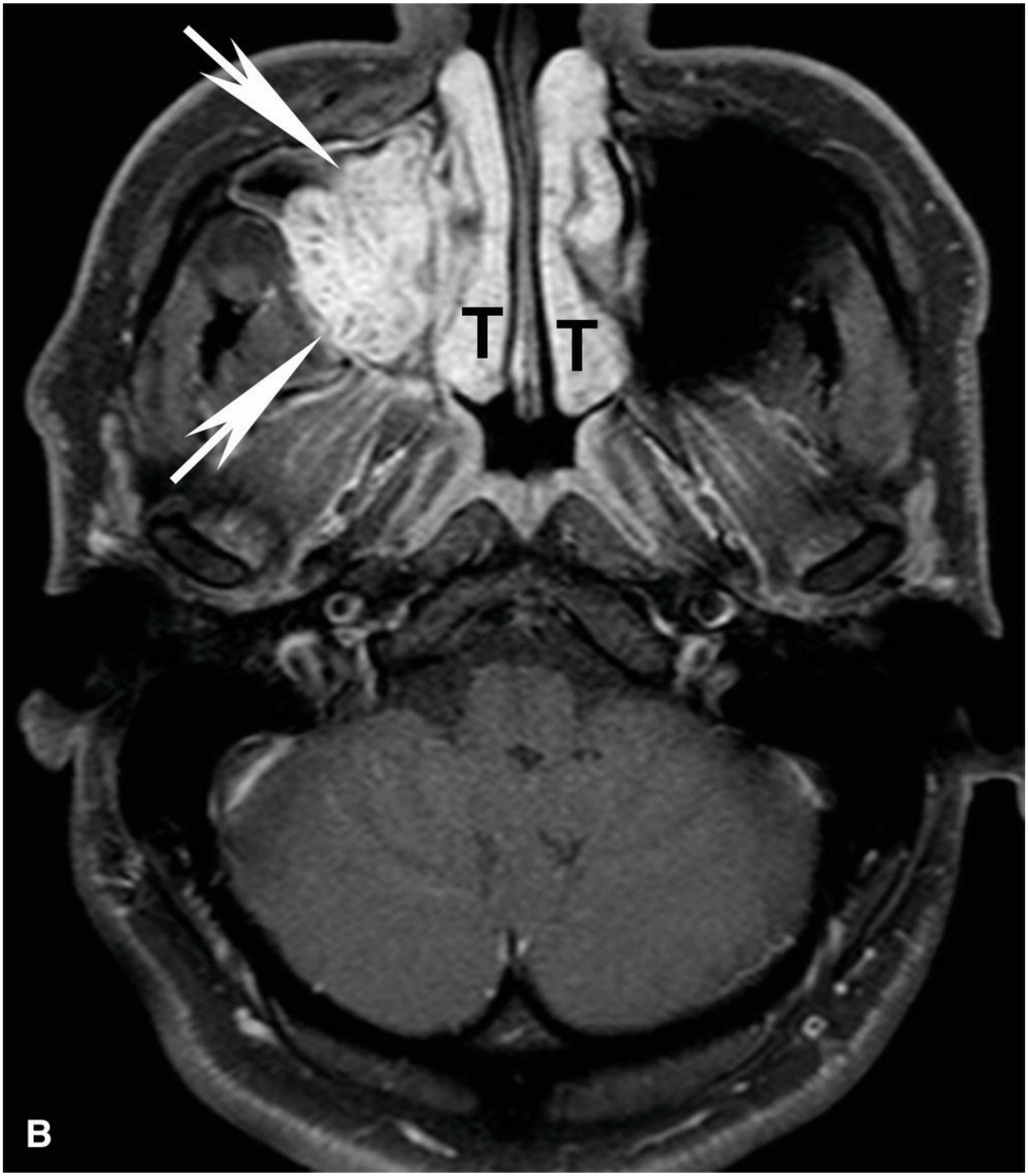

Figure 5.15. Adenoid cystic carcinoma of the maxillary sinus. Coronal T2w **(A)** and axial postcontrast T1w **(B)** fat-suppressed images from a 26-year-old patient. On T2w images, the tumor (*arrows*) is hyperintense to muscle but not strikingly bright. There is only a small amount of secretions and inflammatory mucosal changes on either sides (*arrowheads*), with higher signal than the tumor on T2w images **(A)**. There is heterogeneous but robust

enhancement of the tumor *arrows* in **(B)**. The normal enhancement of the lining of nasal turbinates (T) should not be mistaken for tumor. In cases when tumor abuts the turbinates, this distinction may be more difficult, but careful evaluation of contiguity with the main tumor mass and subtle signal changes on all sequences may be helpful for making the distinction.

On CT, SCCs can appear as homogenous or heterogeneous soft tissue attenuation lesions with variable enhancement[33,34] (Figs. 5.2 to 5.4). There can be areas of internal heterogeneity or necrosis with low attenuation, particularly in larger lesions (Fig. 5.3). On MRI, the soft tissue extent of a tumor may be better seen because of MRI's superior soft tissue contrast compared to CT. On conventional T1w images without fat suppression, SCC has intermediate signal intensity and is generally isointense or hypointense to muscles[35–38] (Fig. 5.6), although rarely it may be slightly hyperintense.[38] On T2w images, SCC is typically isointense to hyperintense relative to normal muscle (but may be hypointense depending on the specific tumor type and cellularity) and can appear heterogeneous[35,37,38] (Fig. 5.16). Similar to CT, SCC has variable enhancement on contrast-enhanced MRI and typically well seen on fat-suppressed T1w images[35–37] (Figs. 5.6, 5.16, and 5.17). It is important to confirm that the high signal represents true enhancement by comparing to the similar sequence obtained before fat suppression.


A

Figure 5.16. Buccal squamous cell carcinoma. Coronal T2w **(A)** and contrast-enhanced fat-suppressed T1w **(B)** images. The mass is heterogeneous and appears hyperintense to muscle on T2w images with heterogeneous enhancement that is greatest around its margins.


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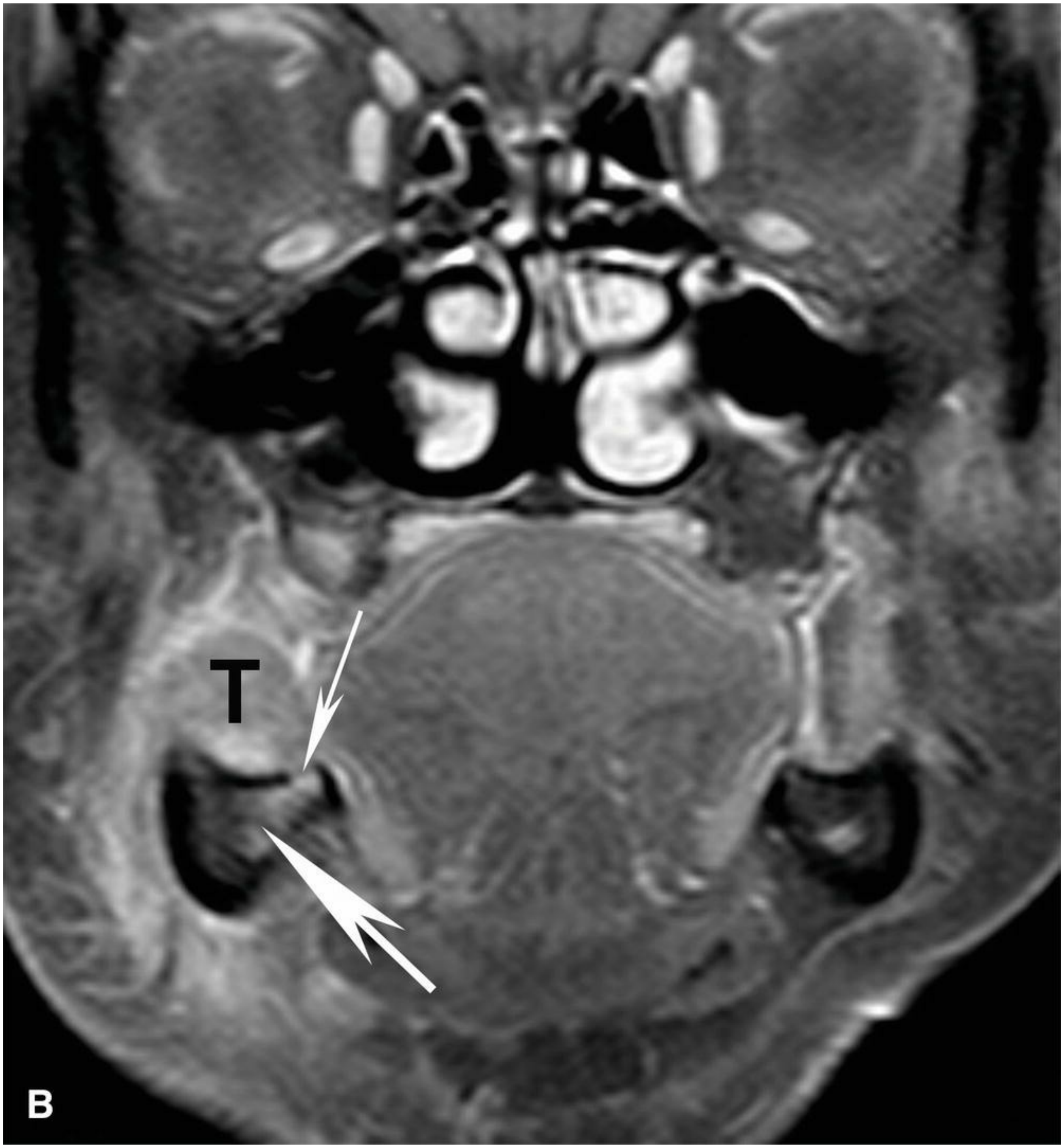
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Figure 5.17. Superficial invasion of the mandibular cortex with reactive marrow edema on MRI. Axial STIR **(A)**, coronal contrast-enhanced fat-suppressed T1w **(B)**, axial T1w **(C)**, and coronal T2w **(D)** MRI images are shown from the same patient whose CT is shown in Figure 5.4. Corresponding to the small focal cortical break seen on CT, there is a potential defect (*thin arrow*), although the MRI is less convincing than the CT. There is also mildly increased signal within the marrow (*thick arrow*) on the STIR **(A)** and contrast-enhanced **(B)** images, demonstrating the increased

sensitivity of MRI for detecting subtle marrow changes. However, in this case, the fat within the marrow is preserved on the T1w image (**C**; *thick arrow*) and the signal is normal on the T2w image (**D**; *thick arrow*). This suggests that the mild signal abnormality represents reactive marrow edema and not true marrow invasion. Pathology confirmed superficial cortical invasion without marrow invasion.

Assessment of tumor density on CT and signal on MRI is only part of the evaluation used to detect tumor and delineate its extent. Assessment for presence of asymmetry is also key for detection of subtle small tumors that may have density or signal similar to adjacent structures (Fig. 5.14). Loss of symmetry in or around a structure can be an important clue to the presence of pathology in that region. Fat represents an important source of intrinsic contrast on both CT and MRI and is clearly distinguishable from soft tissue characteristics of most nonlipomatous tumors. Careful evaluation of infiltration and obliteration/asymmetry in the fat within and fat planes separating various structures and spaces in the neck will enable identification of small tumors and areas of tumor infiltration (Fig. 5.14). Familiarity with the detailed anatomy of the neck is an essential asset to help evaluation. Disruption of normal tissue architecture is also important for evaluating tumor infiltration. For example, the preserved striated architecture of denervated muscle should enable distinction from tumor invasion despite the abnormal signal (Fig. 5.8). By taking into account all the different characteristics, an optimal imaging evaluation and lesion characterization can be performed. Information from the PET scan complements the anatomic information provided on CT and MRI and can increase sensitivity for detection of tumor, lymphadenopathy, and recurrence in head and neck squamous cell carcinoma (HNSCC).[13]

Evaluation of the Primary Site and Local Extent of Tumor (T Stage)

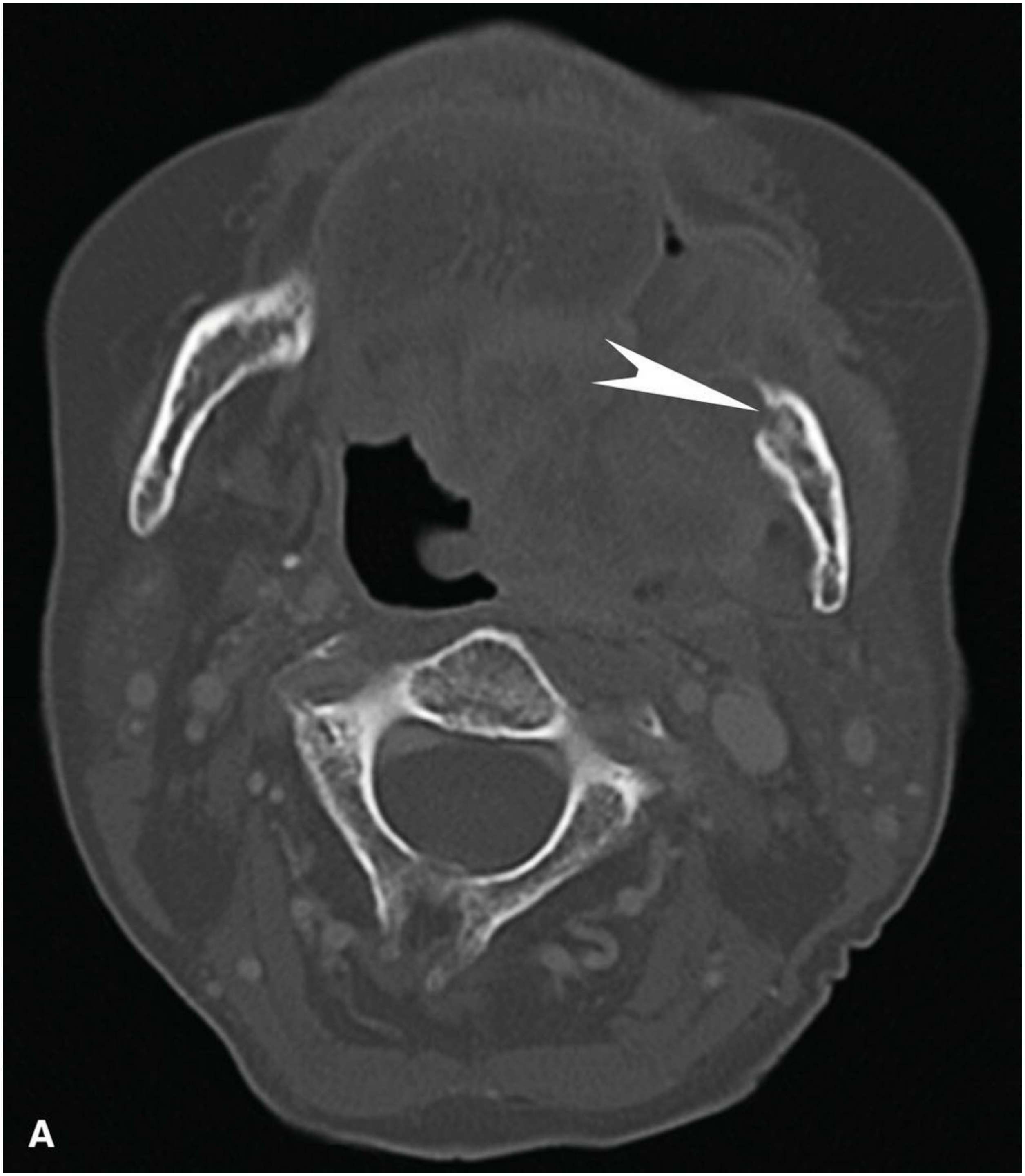
General Evaluation

After identification of the primary tumor, the initial key task of the radiologist is to determine the anatomic extent of the tumor. The T stage indicating the extent of primary tumor will vary depending on the primary

site, and important site-specific determinants of T stage are discussed later for individual primary sites or can be found in the AJCC manual[24] and elsewhere in this book. In this regard, familiarity with the AJCC tumor staging classification and factors altering management, including those important for selection of organ preservation and surgical therapies, is an essential asset for the head and neck radiologist and will enable the radiologist to provide an optimal, clinically relevant imaging evaluation. Regardless of particularities of each primary site, certain general principles apply to all sites.

Evaluation of Bone Invasion

CT and MRI are generally considered complementary in the evaluation of bone invasion by tumor. CT better demonstrates bone detail and architecture and is excellent for evaluation of cortical bone. CT is particularly useful for assessment of subtle cortical bone destruction or periosteal reaction (Figs. 5.4 and 5.18). CT also shows bony landmarks, including those used for surgical planning and intraoperative guidance during sinonasal and skull base surgery. On the other hand, MRI is more sensitive than CT for detection of early marrow invasion and better depicts marrow invasion by tumor (Fig. 5.18). MRI has superior sensitivity to CT in demonstrating marrow edema. This can be an advantage, but care should be taken to make sure the signal is similar to the actual tumor in order not to overcall marrow invasion (Figs. 5.17 and 5.18).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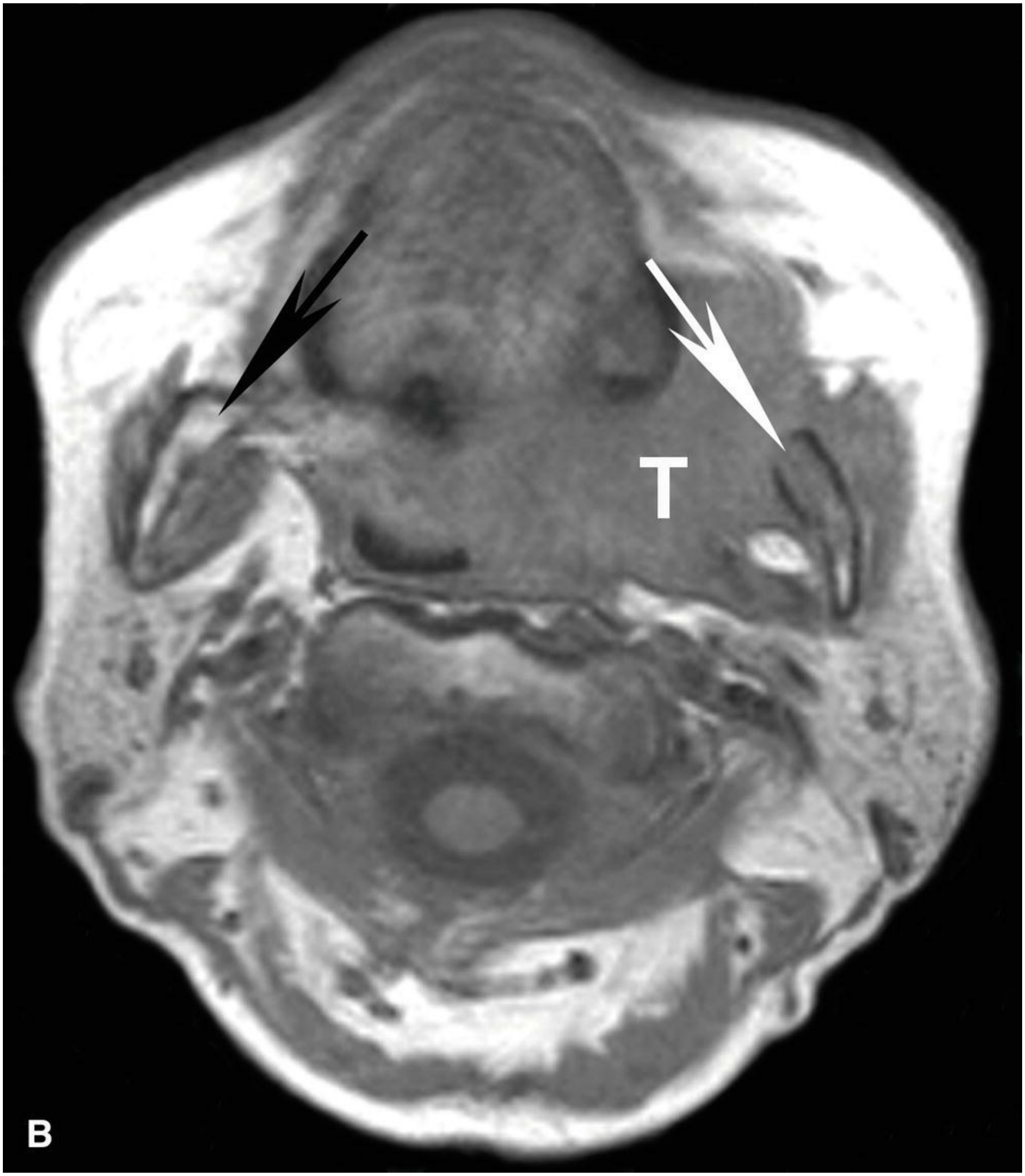
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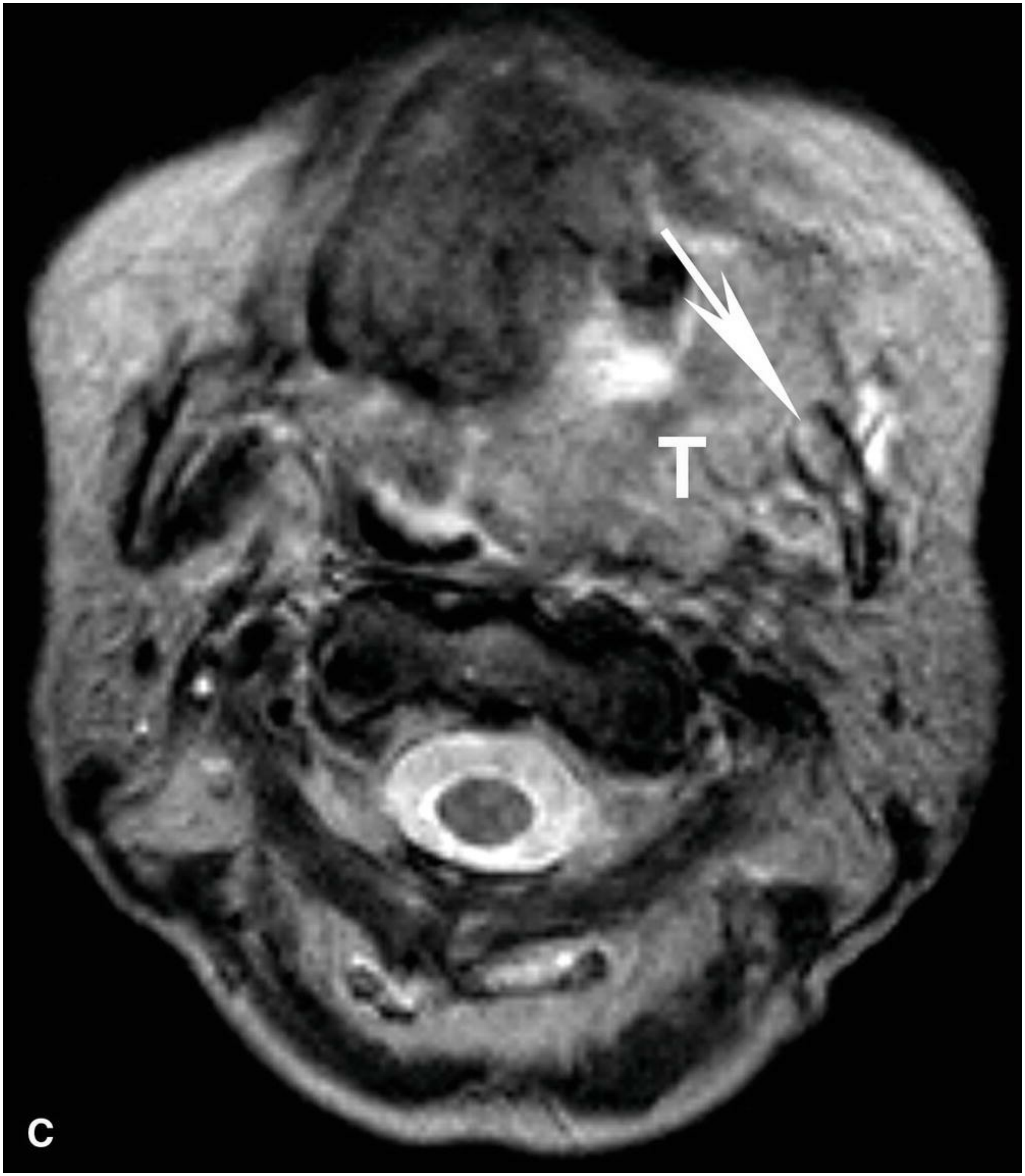
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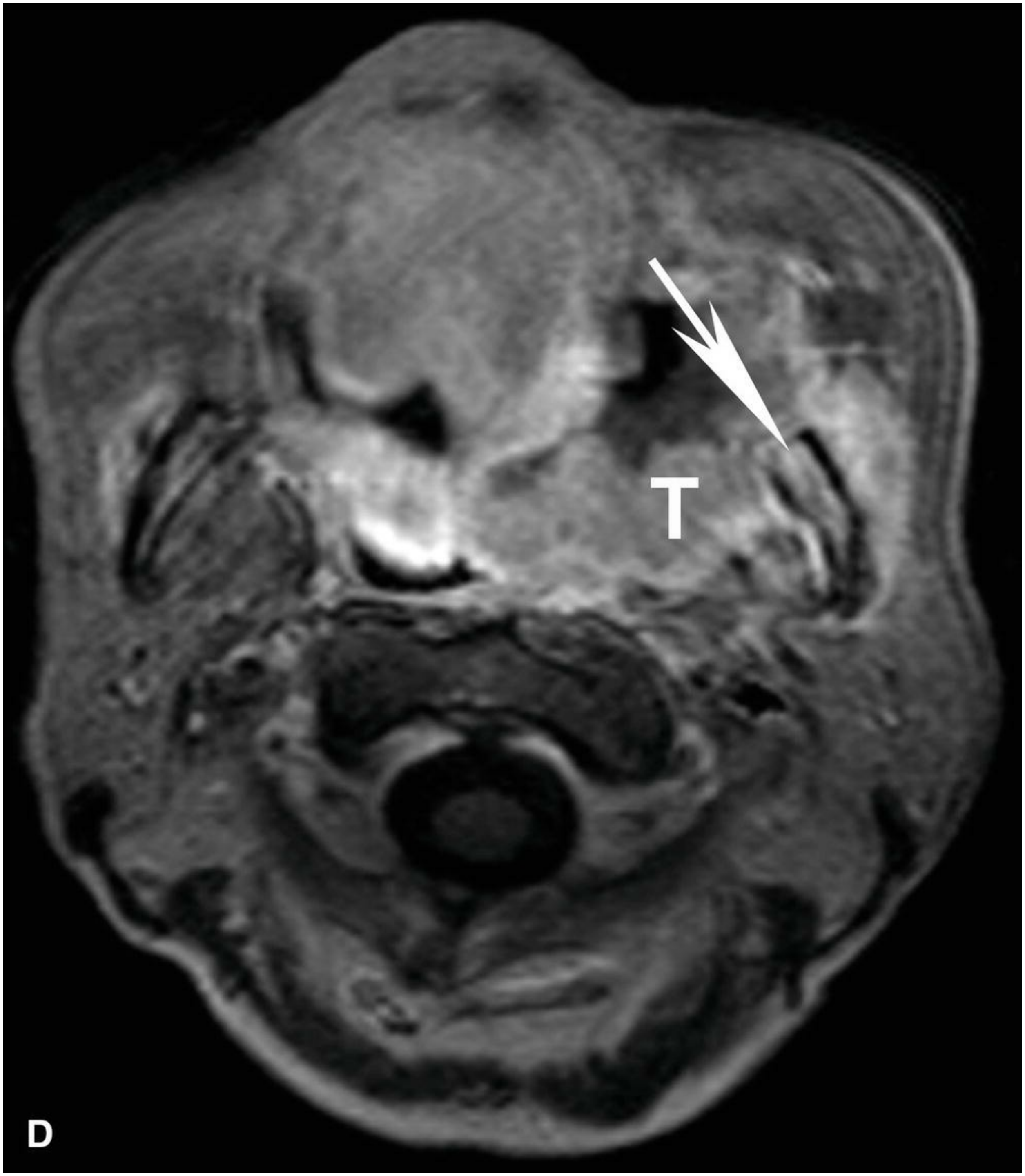

Figure 5.18. Increased sensitivity of MRI for determination of invasion of the bone marrow compared to CT. Axial CT displayed in bone windows **(A)** and unenhanced T1w **(B)**, T2w **(C)**, and contrast-enhanced fat-suppressed T1w **(D)** MRI images are shown from a patient with an advanced squamous cell carcinoma of the retromolar trigone (T) with invasion of multiple adjacent spaces including the buccal space, masticator space, and

oropharynx. On CT, the cortical invasion of the left mandible is subtly evident (*arrowhead*). However, the marrow invasion is not clearly demonstrated. On the MRI, however, there is clear invasion of the marrow with replacement of the normal marrow fat in the mandibular ramus with tumor (*white arrow*). Note the difference compared to the normal marrow of the contralateral mandibular ramus, particularly well seen on the unenhanced T1w image (**B**, *black arrow*). Unlike reactive marrow edema shown in Figure 5.17, the marrow signal abnormality follows the signal of large extraosseous tumor mass on all sequences, a key feature for differentiating the two on imaging.

Evaluation of Arterial Invasion

Invasion of the carotid artery in head and neck cancer portends a poor prognosis[39] and alters management, including surgical approach and assessment for resectability of a lesion. Different imaging criteria have been evaluated for prediction of arterial invasion by tumor.[40–44] In general, if there is >180 degree encasement of the circumference of the artery with loss of fat plane, the possibility of invasion needs to be raised and there is high likelihood of invasion if there is >270 degree encasement.[40]

Role of FDG-PET in the Evaluation of Untreated Primary Tumor Local Extent and T Stage

Most HNSCCs are well visualized by CT and MRI during initial tumor evaluation, and CT and MRI are superior to PET alone for evaluation of detailed anatomy and tumor extent. Therefore, even though PET has high accuracy in detecting the primary lesion, typically, it does not add significant clinically useful information to CT/MRI for determination of the local anatomic extent/T stage of the tumor.[14] However, in cases of equivocal findings, PET may be helpful and should be considered. In cases of carcinomas of unknown primary, there is currently no consensus on the role of PET. Although some studies have reported that the addition of PET improves detection of the occult primary HNSCC,[20] PET does not have sufficient sensitivity or negative predictive value to exclude a primary. In particular, PET has low sensitivity for detection of primary cancers arising in the oropharynx because of the relatively high background physiologic

activity within the Waldeyer ring structures[14] (Figs. 5.11 and 5.12).

Evaluation of Lymphatic Spread of Tumor (N Stage)

Overview

Determination of the presence of nodal metastasis is also essential for proper staging and surveillance of head and neck cancer. In the AJCC classification, there is a uniform N classification system for cervical lymph node metastasis from all primary sites except for those arising from the nasopharynx, thyroid, and skin cancers; nasopharyngeal carcinoma has a separate nodal staging classification.[24] Imaging plays an important role in evaluation of lymph nodes, enabling confirmation of clinically suspected lymphadenopathy and evaluation of deeper nodal levels that cannot be reliably evaluated on clinical examination.[45–47] Optimal evaluation for the presence of lymphadenopathy requires an understanding of the strengths and limitations of imaging criteria used for determination of nodal metastases. In equivocal cases, image-guided (usually US) biopsy can be used for a more definitive assessment. In addition, it is important to be aware that although imaging is useful for staging a tumor, imaging cannot reliably exclude micrometastases to lymph nodes, especially for tumors of the oral cavity. It is worth emphasizing that potentially abnormal nodes should be interpreted in the context of their location with respect to a known or suspected primary malignancy; their size, shape, and number; or presence of focal internal defect. As such, isolated interpretation based solely on the appearance of lymph nodes on an imaging study is fraught with pitfalls and is discouraged.[45–47]

Imaging-Based Anatomic Classification of Lymph Nodes

When evaluating cervical lymph nodes, the first step is the proper anatomic localization of a lymph node. Earlier lymph node classification systems were based on clinical landmarks.[45–48] However, with improvements in imaging techniques enabling accurate identification of enlarged lymph nodes and a shift in treatment paradigm in which many cancers were not treated surgically, an imaging-based classification system represented the most practical and logical approach. The imaging-based classification system

proposed by Som et al.[49] is a level-based classification and has received widespread acceptance, including adoption by the AJCC. The rationale behind this classification system is to provide a reproducible, widely applicable framework based on readily identifiable imaging landmarks.

In the imaging-based classification, the cervical nodal chains are divided into seven levels.[45]–[49] The levels and the landmarks used for the classification are described in detail in Table 5.4 and illustrated in Figure 5.19. Briefly, level I consists of submental (IA) and submandibular (IB) nodes. Levels II to IV consist of internal jugular nodes. Level II nodes extend from the skull base to the level of the lower body of the hyoid bone. Level II is further subclassified into levels IIA (anterior) and IIB (posterior to the internal jugular vein and separated from it by a fat plane). Level III nodes consist of those nodes that are around the internal jugular vein, between the level of the lower body of the hyoid bone and the level of the lower margin of the cricoid cartilage arch. Level IV nodes are internal jugular chain nodes that extend from the level of the lower margin of the cricoid cartilage arch to the level of the top of the manubrium. Level V nodes are posteriorly located lymph nodes that are subdivided into levels VA and VB. Level VI nodes are the visceral nodes, and level VII nodes are those that lie caudal to the top of the manubrium, located between the medial margins of the left and right common carotid arteries in the substernal region[45]–[47] (Fig. 5.19; Table 5.4). Please refer to Table 5.4 for a detailed description of the anatomic landmarks used for the imaging classification.

Table 5.4 Landmarks Used for Cervical Lymph Node Localization Using the Imaging-based Classification

Node Levels	Major Landmarks	Sub-Classifications
Level I	All of the nodes below the mylohyoid muscles, anterior to a transverse line drawn through the posterior edge of the submandibular gland in the axial plane, and above the bottom of the body of the hyoid bone.	*Level IA* Nodes that lie between the medial margins of the anterior bellies of the digastric muscles (previously classified as submental nodes)
	These include previously classified submental and submandibular nodes.	*Level IB* Nodes that lie posterior and lateral to the medial edge of the anterior belly of the digastric muscle (previously classified as submandibular nodes)
Level II	Nodes around the internal jugular vein extending from the lower bony margin of the jugular fossa at the skull base to the level of the lower body of the hyoid bone.	*Level IIA* Nodes that lie anterior, lateral, or medial to the internal jugular vein (previously classified as upper internal jugular nodes) as well as nodes that lie posterior to the internal jugular vein and are *inseparable* from the vein
	Nodes that lie anterior to a transverse line drawn on each axial image through the posterior edge of the sternocleidomastoid muscle, and posterior to a transverse line drawn on each axial scan through the posterior edge of the submandibular gland.	
	In the area within 2–3 cm of the skull base, a node located anterior, lateral, or posterior to the internal carotid artery is classified as a level II node. However, if the node lies medial to the internal carotid artery, it is classified as a retropharyngeal node. More caudally, level II nodes include those located anterior, lateral, medial, or posterior to the internal jugular vein.	*Level IIB* Nodes that lie posterior to the internal jugular vein and are separated from the vein by a fat plane (previously classified as upper spinal accessory nodes). These nodes are located in the fat deep to the sternocleidomastoid muscle.
Level III	Nodes around the internal jugular vein between the level of the lower body of the hyoid bone and the level of the lower margin of the cricoid cartilage arch.	
	These nodes lie anterior to a transverse line drawn on each axial image through the posterior edge of the sternocleidomastoid muscle.	
	Level III nodes also lie lateral to the medial margin of either the common carotid artery or the internal carotid artery. On each side of the neck, the medial margin of carotid arteries separates level III nodes (located laterally) from level VI nodes (located medially).	
Level IV	Nodes around the internal jugular vein between the level of the lower margin of the cricoid cartilage arch and the level of the top of the manubrium.	
	These nodes lie anterior and medial to an oblique line drawn through the posterior edge of the sternocleidomastoid muscle and the lateral posterior edge of the anterior scalene muscle.	
	The medial margin of the common carotid artery is the landmark that separates level IV nodes (located laterally) from level VI nodes (located medially).	
Level V	Nodes extending from the skull base, at the posterior border of the attachment of the sternocleidomastoid muscle, to the level of the clavicle, as seen on each axial scan.	*Level VA* Nodes between the skull base and the level of the lower margin of the cricoid cartilage arch, behind the posterior edge of the sternocleidomastoid muscle
	All these nodes lie anterior to a transverse line through the anterior edge of the trapezius muscle in the axial plane.	
	From the skull base to the bottom of the cricoid arch, these nodes are located posterior to a transverse line through the posterior edge of the sternocleidomastoid muscle in the axial plane (VA). More caudally, between the level of the bottom of the cricoid arch and top of the manubrium, they lie posterior and lateral to an oblique line through the posterior edge of the sternocleidomastoid muscle and the lateral posterior edge of the anterior scalene muscle (VB).	*Level VB* Nodes between the lower margin of the cricoid cartilage arch and the level of the clavicle, as seen on each axial scan. They are behind an oblique line through the posterior edge of the sternocleidomastoid muscle and the lateral posterior edge of the anterior scalene muscle.
Level VI	Nodes located between the medial margins of the left and right common carotid or internal carotid arteries, extending from the level of the lower body of the hyoid bone to the level superior to the top of the manubrium. These are the visceral nodes.	
Level VII	Nodes in the substernal region extending from the level of the top of the manubrium to the level of the innominate vein, between the medial margins of the left and right common carotid arteries	

Adapted from Forghani R, Yu E, Levental M, et al. Imaging evaluation of lymphadenopathy and patterns of lymph node spread in head and neck cancer. *Expert Rev Anticancer Ther*. 2015:15(2):207–224.

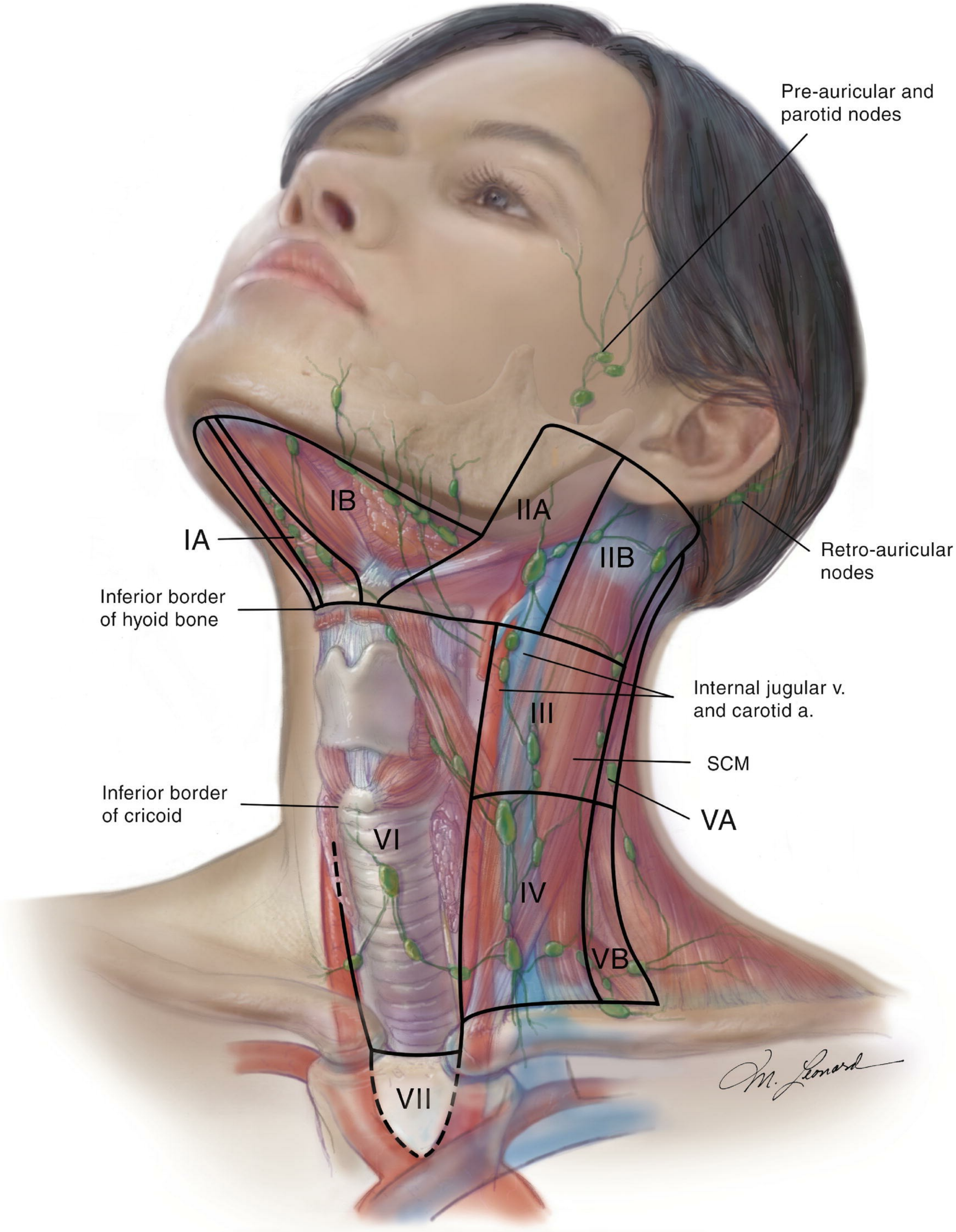

Figure 5.19. Illustration demonstrating the imaging-based classification of cervical lymph nodes. (Illustration is based on the classification proposed by Som PM, Curtin HD, Mancuso AA. An imaging-based classification for the

cervical nodes designed as an adjunct to recent clinically based nodal classifications. *Arch Otolaryngol Head Neck Surg.* 1999;125:388–396; reproduced with permission from Forghani Medical Services Inc.)

It is noteworthy that surgically, levels IIA and IIB are separated by the spinal accessory nerve, the preservation of which reduces morbidity associated with level II compartment dissection.[50] As such, there is some controversy regarding the clinical applicability of separation of level II into radiologic sublevels IIA and IIB.[32] Outside node levels I to VII, other lymph nodes are referred to by their anatomic names. These include the retropharyngeal nodes and the superficial nodes of the neck including the parotid (periparotid and intraparotid), buccinator (facial), suboccipital, and preauricular nodes, among others. The supraclavicular nodes are still frequently referred to by their classic anatomic names because the terminology is deeply entrenched in clinical practice. The supraclavicular fossa is difficult to precisely identify in the axial plane because it is oblique to that plane and not seen in its entirety on a single section. However, it can be approximated on axial images whenever any portion of the clavicle is identified on one side of the neck, provided the patient's shoulders are as low as possible. Using the imaging classification, this would include the caudal portions of the level IV and VB nodes.[45–47]

Imaging Approach and Morphologic Criteria for Assessment of Metastatic Nodes

CT and MRI are almost equivalent for evaluation of metastatic lymphadenopathy, although at least one study has suggested that CT may be slightly superior.[51] In practice, the selection of the imaging modality is based on the primary site and was discussed earlier. US has also been used for evaluation of cervical lymphadenopathy but is operator dependent and does not provide a reliable evaluation of deep nodal levels. As a result, except for thyroid cancer, US is not routinely used for staging of head and neck cancers, though in some centers, it is considered complimentary or useful for cases in which other imaging is equivocal. However, US-guided biopsy is very useful for evaluation of indeterminate nodes. In general, the morphologic criteria used for identification of metastatic nodes are applicable to all three imaging modalities.

Normal nodes are only a few millimeters in size and have smooth well-defined borders on imaging.[45–47] Normal nodes are usually lima bean shaped, although this may not be clearly evident for small nodes and depending on the plane of section used to evaluate that lymph node. Normal nodes also have a fatty hilum, and depending on its size, it may or may not be seen on CT and MRI. Nodes at levels IIA and IB constitute the primary drainage routes of the oral cavity and oropharynx and as a result are frequently exposed to the numerous infections that occur at those sites. Therefore, these nodes are in general larger than other cervical lymph nodes.

The main imaging criteria used for identification of metastatic nodes are node size, internal nodal architecture, nodal grouping or clustering, and node shape and contour[45–47] (Fig. 5.20; Tables 5.5 and 5.6). An optimal evaluation of lymph nodes is performed only when all of these parameters are taken into account, as well as the clinical context, and one should try to avoid focusing excessively on a single parameter such as size in isolation.


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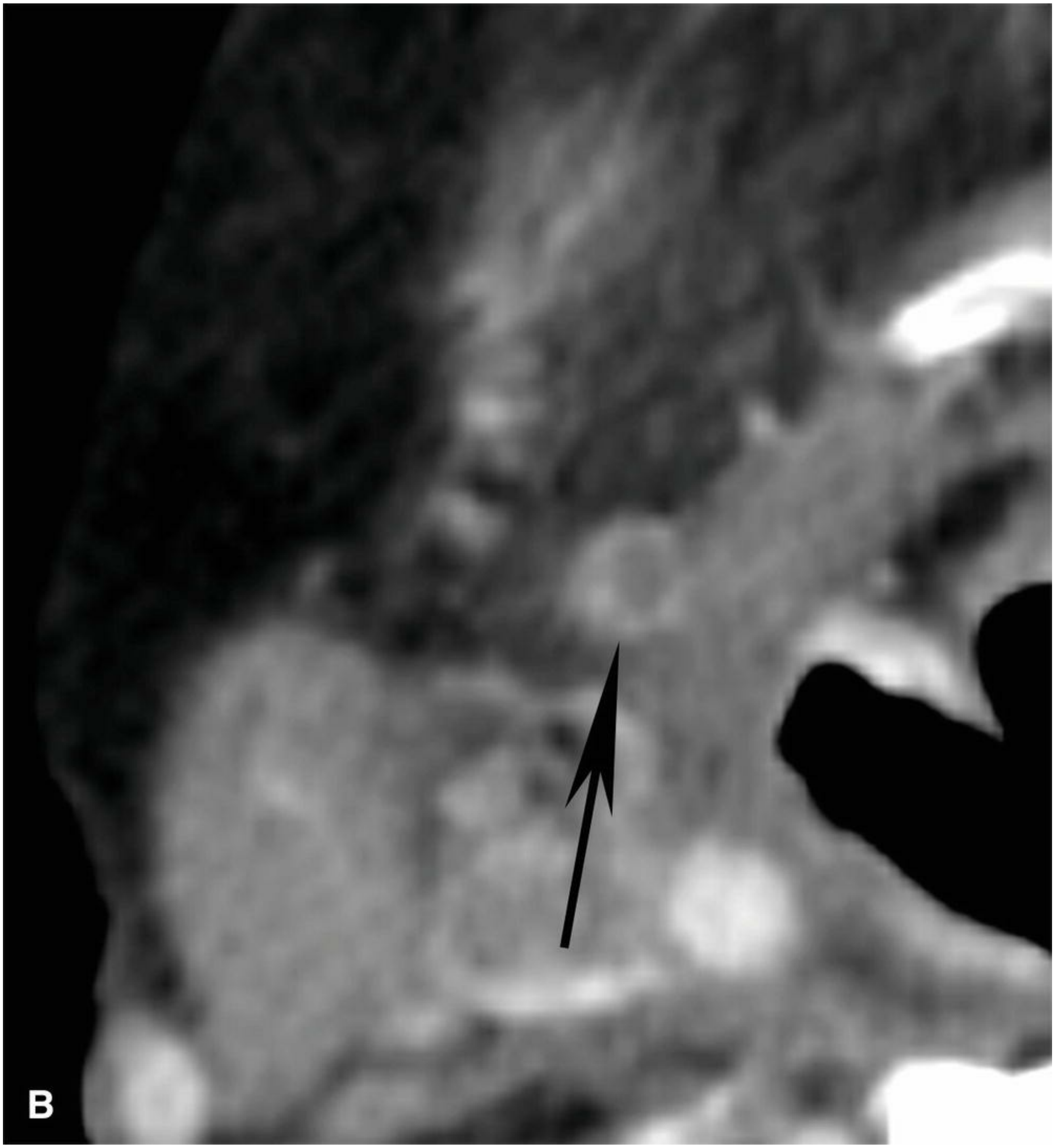
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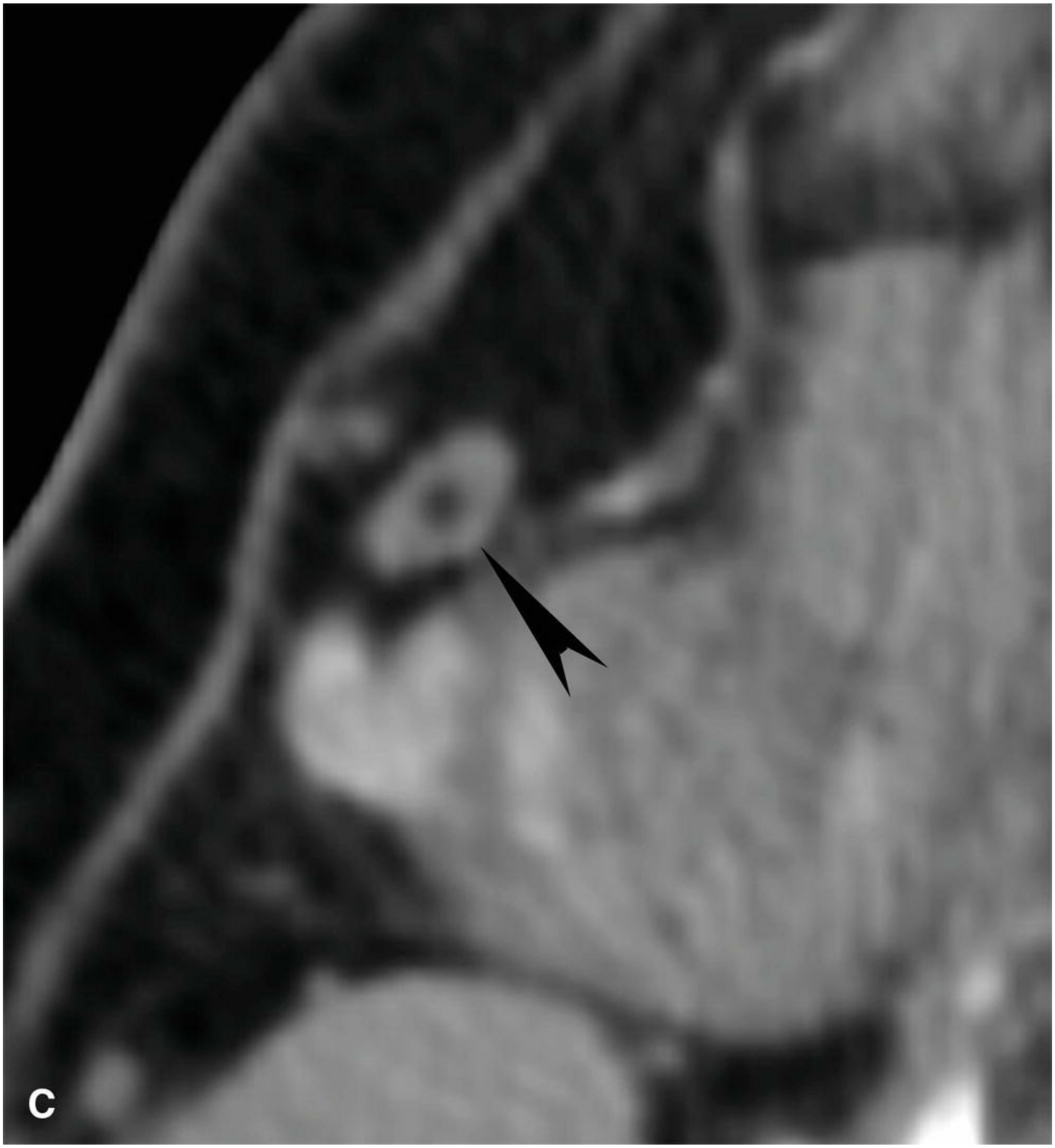


Figure 5.20. Characteristics of metastatic nodes as well as normal fatty hilum. **A:** Axial contrast-enhanced CT image demonstrates different features of pathologic nodes. The large midline node (*arrow*) is rounded and has internal inhomogeneity/necrosis and irregular margins. The more laterally located node (*arrowhead*) on the right is rounded. **B:** Example of small necrotic lymph node (*arrow*). **C:** Example of normal fatty hilum (*arrow*). At this size, the density is clearly identifiable as that of fat (compare to adjacent

subcutaneous fat), and this should not be misinterpreted as nodal necrosis.

Table 5.5 Commonly Used Size Criteria for Distinction of Pathologic from Normal or Benign Reactive Lymph Nodes on Axial Images for Single Homogenous Sharply Delineated Nodes

Short-axis diameter for individual, nonclustered lymph nodes:
Jugulodigastric (level II) nodes Abnormal: ≥11 mm
Retropharyngeal nodes Abnormal: ≥5 mm
All other nodes Abnormal: ≥10 mm
Long-axis diameter for individual, nonclustered lymph nodes:
Jugulodigastric (level II) and submandibular (level I) nodes Abnormal: >15 mm
Retropharyngeal nodes Normal: 8 mm or less, abnormal: >8 mm
All other nodes Normal: 10 mm or less, abnormal: >10 mm
Short-axis diameter for a cluster or group of nodes in the drainage area of the primary tumor site[a] (for nodes other than retropharyngeal nodes):
Jugulodigastric (level II) nodes Abnormal: ≥9–10 mm
Other nodes Abnormal: ≥8–9 mm
Error rates and limitations:
Regardless of the size criterion used, the overall error rates for false-positive and false-negative diagnoses are in the range of ~15% and 20%, reflecting the limitations of the use of size criteria alone for determination of nodal metastasis.

[a]Nodal clustering or grouping is defined as the presence of three or more borderline lymph nodes in the first or second lymph node drainage region of a primary tumor site. When

present, the size threshold for metastatic lymphadenopathy for clustered nodes can be decreased by 1 to 2 mm, increasing sensitivity, without significantly affecting specificity.

Adapted from Forghani R, Yu E, Levental M, et al. Imaging evaluation of lymphadenopathy and patterns of lymph node spread in head and neck cancer. *Expert Rev Anticancer Ther*. 2015;15(2):207–224.

Table 5.6 Imaging Approach and Main Criteria Used for Determination of Metastatic Lymphadenopathy (the Criteria May Be Remembered Using the Acronym CRISPS)

Size (CRISPS) Different criteria can be used. Maximal short-axis diameter may be the most effective criterion (summarized in Table 5.3).
Nodal clustering or grouping (CRISPS) Presence of three or more borderline lymph nodes in the first or second lymph node drainage region of a primary tumor site
Internal architecture: Evaluation of nodal inhomogeneity or necrosis (CRISPS) When >3 mm in size, focal internal inhomogeneity can frequently be identified on CT and MRI and represents the most reliable imaging finding of nodal metastasis in the right clinical context (known or suspected head and neck cancer, absence of infectious symptoms, or suppurative lymphadenitis). Pitfalls/mimics: normal fatty hilum of the node, fatty hilar metaplasia, or an intranodal abscess.
Node morphology: Rounded Shape (CRISPS) Loss of normal elongated shape with rounded appearance of the node Longest axis (any plane)/shortest diameter ratio <2
Node contour or periphery (CRISPS) and extracapsular spread Thickened enhancing rim with infiltration of the adjacent fat planes or soft tissue structures in the absence of recent infection or treatment such as irradiation or surgical manipulation
Sentinel node (CRISPS) Awareness of the main primary and secondary drainage areas for an expected cancer site can heighten suspicion for the presence of metastases and can be used in conjunction with other features to increase confidence or suspicion for the presence of metastases
Clinical context Highest accuracy will be achieved when the clinical context and patient demographics are taken into account. An enlarged or inhomogenous lymph node in an otherwise healthy young patient is most likely to represent an inflammatory, reactive, or infected node, whereas the same node in a patient with known HNSCC is most likely to represent a metastatic lymph node.
Others Evaluate metabolic activity and uptake on PET when available; image-guided biopsy can be used for evaluation of borderline and indeterminate nodes.

Adapted from Forghani R, Yu E, Levental M, et al. Imaging evaluation of lymphadenopathy and patterns of lymph node spread in head and neck cancer. *Expert Rev Anticancer Ther*. 2015;15(2):207–224.

On imaging, node size is typically evaluated in the axial plane because this is most practical, and a convincing advantage for measurements in other planes has not been shown. Either the short-axis or the long-axis diameter may be used for evaluation of metastatic nodes, although in one large prospective study, the short-axis diameter was reported as the most effective size criterion.[52] The commonly accepted size criteria for evaluation of metastatic lymph nodes are summarized in Table 5.5. It is important to note that all the proposed size criteria apply to *homogenous, sharply delineated nodes*. Neither of the size criteria is perfect with overall estimated error rates of ~15% and 20%.[45–47]

The first lymph node or group of nodes draining a primary site are at the highest risk of harboring metastases and lower threshold for additional investigation or biopsy of indeterminate or borderline nodes in these areas.[46,53] When a cluster of borderline enlarged nodes, defined as three or more lymph nodes in the drainage area of the primary tumor site, is present, the short-axis size threshold can be decreased by 1 to 2 mm, increasing sensitivity without affecting specificity[45–47,52] (Table 5.5).

Tumor infiltration of a lymph node can result in intermixed areas of tumor, edema, necrosis, and residual normal node tissue. As a result, metastatic nodes can appear nonhomogenous (Fig. 5.20; Table 5.5). On imaging, this can result in areas of relatively low attenuation on CT or high signal on T2w and STIR images and is referred to as necrosis or internal inhomogeneity. If the focus of internal abnormality is >3 mm in size, it is frequently identifiable on CT (Fig. 5.20) and MRI and represents the most reliable imaging sign of nodal metastasis in the *appropriate clinical context*, that is, patients with suspected or biopsy-proven head and neck cancer.[45–47,52,54,55] The inhomogeneity may be central or peripheral in the subcapsular region. The differential diagnosis of internal nodal inhomogeneity that should not be mistaken for is the normal fatty hilum of the node or reactive fatty hilar metaplasia (Fig. 5.20) or an intranodal abscess/suppurative lymphadenitis.

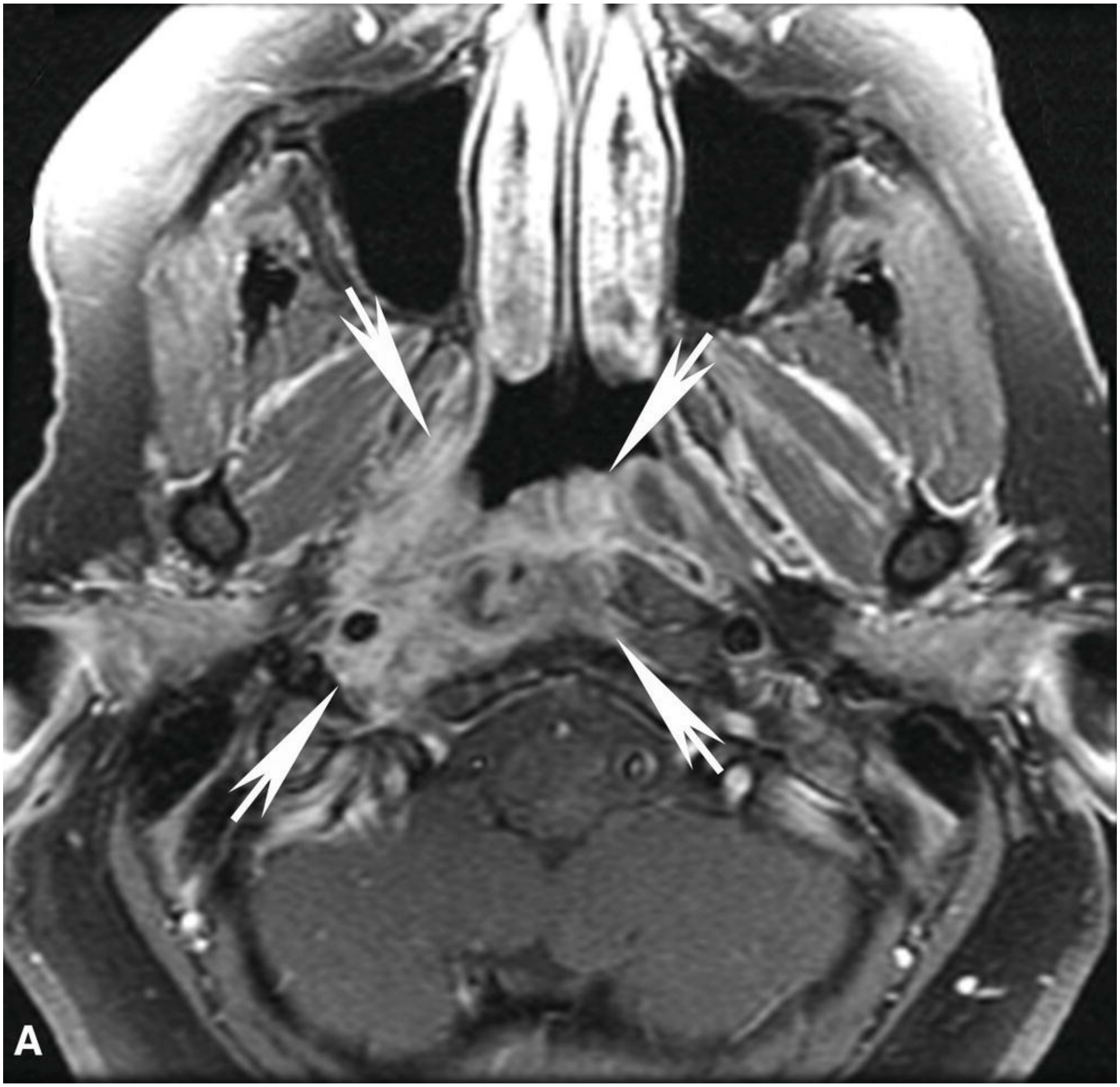
Other characteristics that can be used for evaluation of metastatic nodes are node shape and contour (or periphery). Normal nodes tend to be oblong elliptical or “lima bean”–shaped structures, whereas metastatic nodes tend to become rounded and spherical (Fig. 5.20). Unfortunately, depending on their location in the neck and the plane in which the node is assessed, this criterion may not be reliably applied to small lymph nodes. Normal nodes also typically have a smooth well-defined contour. Therefore, unless there has been treatment such as radiation therapy or neck surgery, contour irregularity is suggestive of pathology (Fig. 5.20). Transgression of tumor across the node capsule into the adjacent soft tissues is referred to as extracapsular, extranodal, or transcapsular spread of tumor (ECS). The presence of ECS is associated with an increased risk of tumor recurrence, distant metastases, and a decrease in patient survival.[56,57] On imaging, macroscopic ECS appears as infiltration of the adjacent fat planes or soft tissues, although this is not always present in histologically verified ECS, or may be present in the absence of ECS. Spread to adjacent anatomic structures should be identified, especially encasement of critical structures such as muscles or the carotid artery, which may indicate nonresectability.

Role of FDG-PET for the Evaluation of Nodal Metastases and N Stage

PET can detect metastases in small nodes that may otherwise appear normal on CT or MRI by demonstrating increased metabolic activity (Figs. 5.10 and 5.11). The addition of PET to conventional anatomic techniques such as CT and MRI increases sensitivity for detection of nodal metastases and can upstage the N stage by 15% to 20%.[13,14] In a recently published evidence-based guidelines, PET was recommended for nodal staging in patients with equivocal findings on conventional imaging.[58] Of course, one must be aware of pitfalls of PET, both false negatives such as in the evaluation of necrotic nodes (Fig. 5.10) and false positives, discussed earlier in this chapter. It is important to be aware that detection of metastases in small lymph nodes remains a challenge even with PET, particularly in lymph nodes measuring <7 mm. PET is not sufficiently sensitive to preclude an elective neck dissection in head and neck cancers with a high risk of occult metastases.[46]

Perineural Spread of Tumor

PNS of tumor is a well-recognized mode of tumor dissemination in head and neck cancer.[25,26] In PNS, tumor spreads from the primary site along the nerve and nerve sheath. PNS should be distinguished from perineural invasion (PNI), which refers to microscopic involvement of small nerves at the site of primary tumor on histology.[26,59,60] In PNS, tumor extends beyond the site primary tumor with large nerve involvement and can be thought of as a mode of metastasis.[26] Many head and neck tumors may have associated PNS including mucosal SCCs, salivary gland malignancies (in particular adenoid cystic carcinoma [Fig. 5.21]), and cutaneous malignancies such as SCC and desmoplastic melanoma. Other neoplasms that may present with PNS include NPC.[26] Adenoid cystic carcinoma has the greatest propensity for PNS, but given the much higher incidence of SCC, that tumor more commonly presents with PNS. PNS of tumor is typically retrograde, toward the central nervous system, but there can also be antegrade spread away from the CNS. Branches of the trigeminal and facial nerves are most commonly affected by PNS although other nerves may be affected as well depending on the primary tumor site. Because a significant percentage of patients with PNS may be asymptomatic initially, its detection requires heightened awareness and vigilance on the part of the radiologist in order to make a timely diagnosis.[25,26]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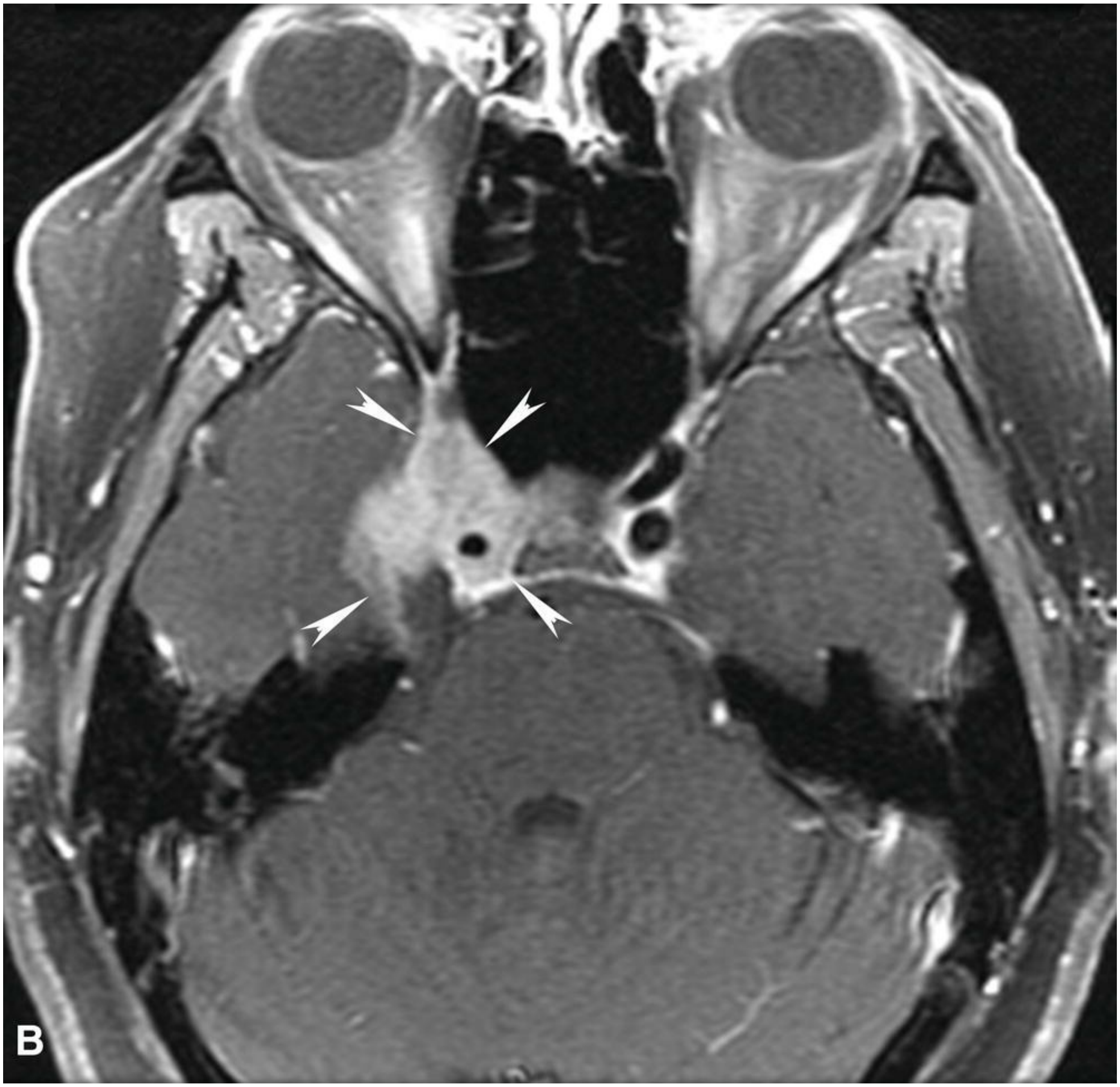
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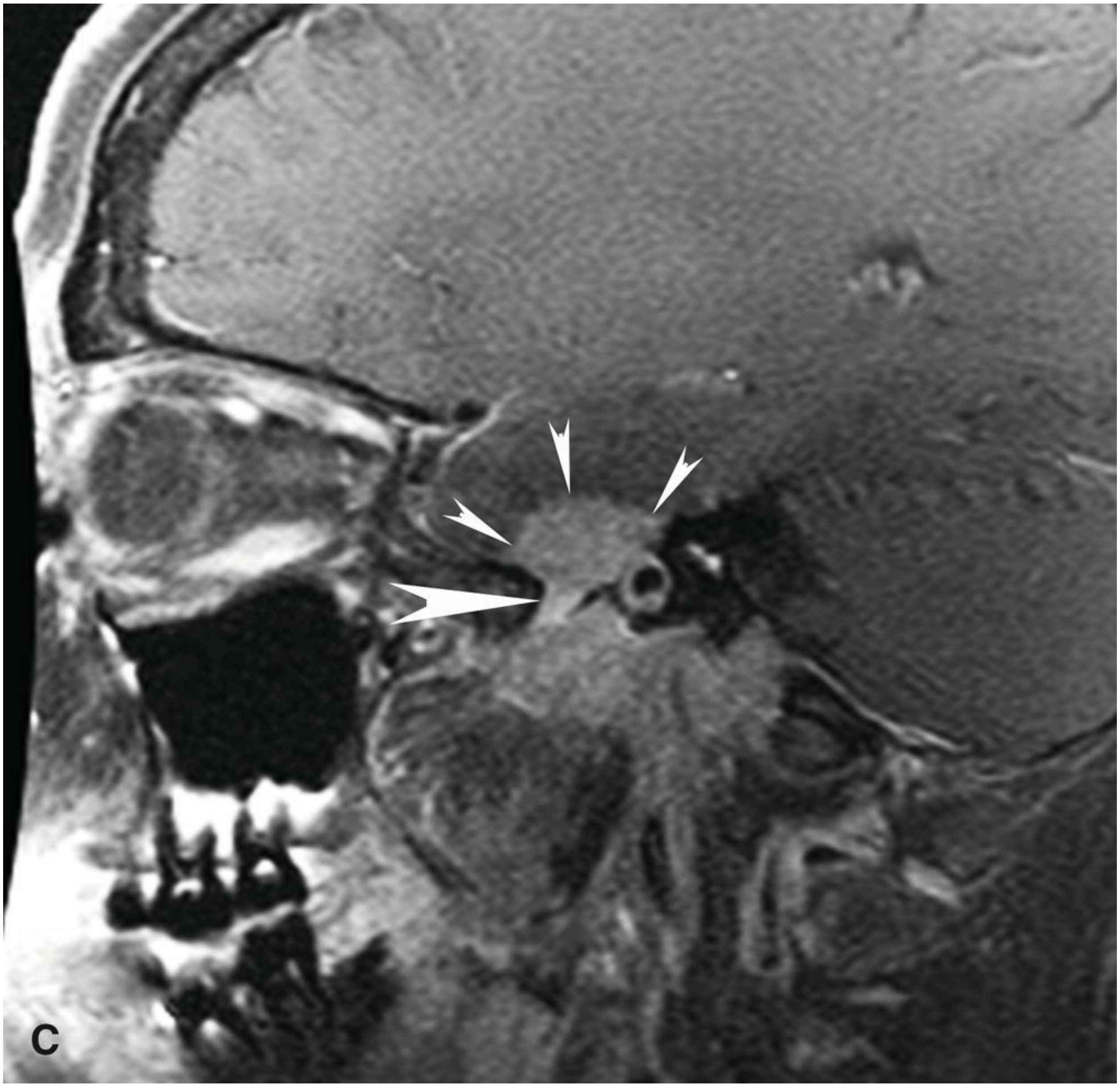
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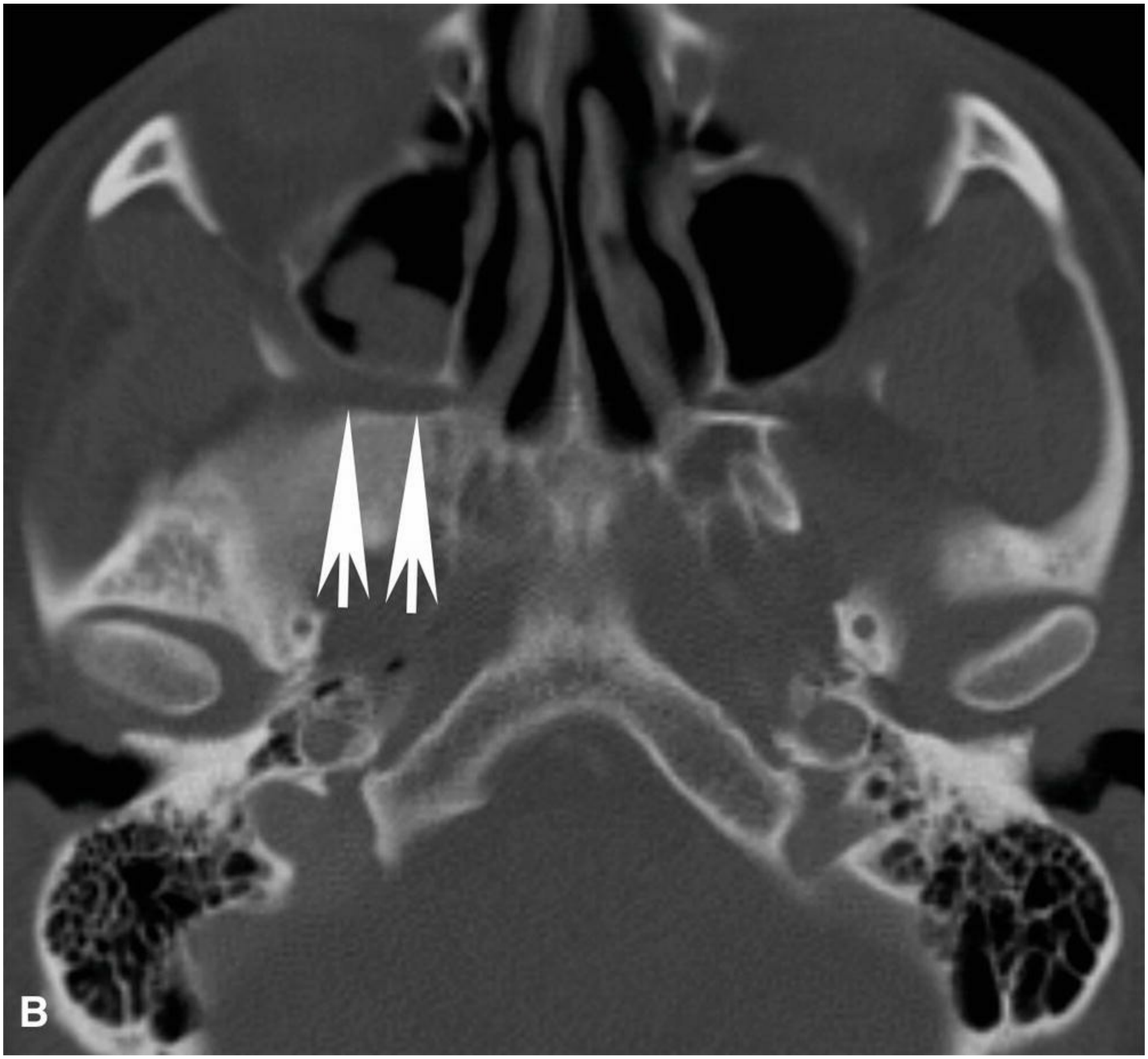
Figure 5.21. Adenoid cystic carcinoma of the nasopharynx with PNS of tumor and intracranial spread. Axial **(A, B)**, sagittal **(C)**, and coronal **(D)** contrast-enhanced fat-suppressed T1w MRI images are shown. There is an infiltrative nasopharyngeal tumor (**A**; *arrows*), the bulk of which is on the right side. There is PNS through the right foramen ovale (**C,D**; *large arrowhead*) with spread of tumor into the right middle cranial fossa and cavernous sinus (**B–D**; *small arrowheads*).

On CT, PNS can present as subtle infiltration of fat surrounding the nerve in different foramina or spaces such as the pterygopalatine fossa (PPF) (Fig. 5.22) or in the stylomastoid foramen. There can also be expansion and

remodeling of the foramina or surrounding bones (Fig. 5.22), or destruction of bone in late cases. However, PNS is much better seen on MRI[25,26] (Figs. 5.21 and 5.22). On T1w images, PNS will manifest as replacement and obliteration of normally bright fat in the PPF (Fig. 5.22) or fat surrounding the nerves within different foramina. On fat-suppressed contrast-enhanced images, enhancing tumor is clearly distinguishable from surrounding fat (Figs. 5.21 and 5.22). The involved nerve may appear expanded, but this is not an absolute requirement for diagnosis, and asymmetric enhancement of a nerve alone can suggest the presence of PNS in the absence of other explanation such as nonspecific neuritis or benign lesions of the nerve.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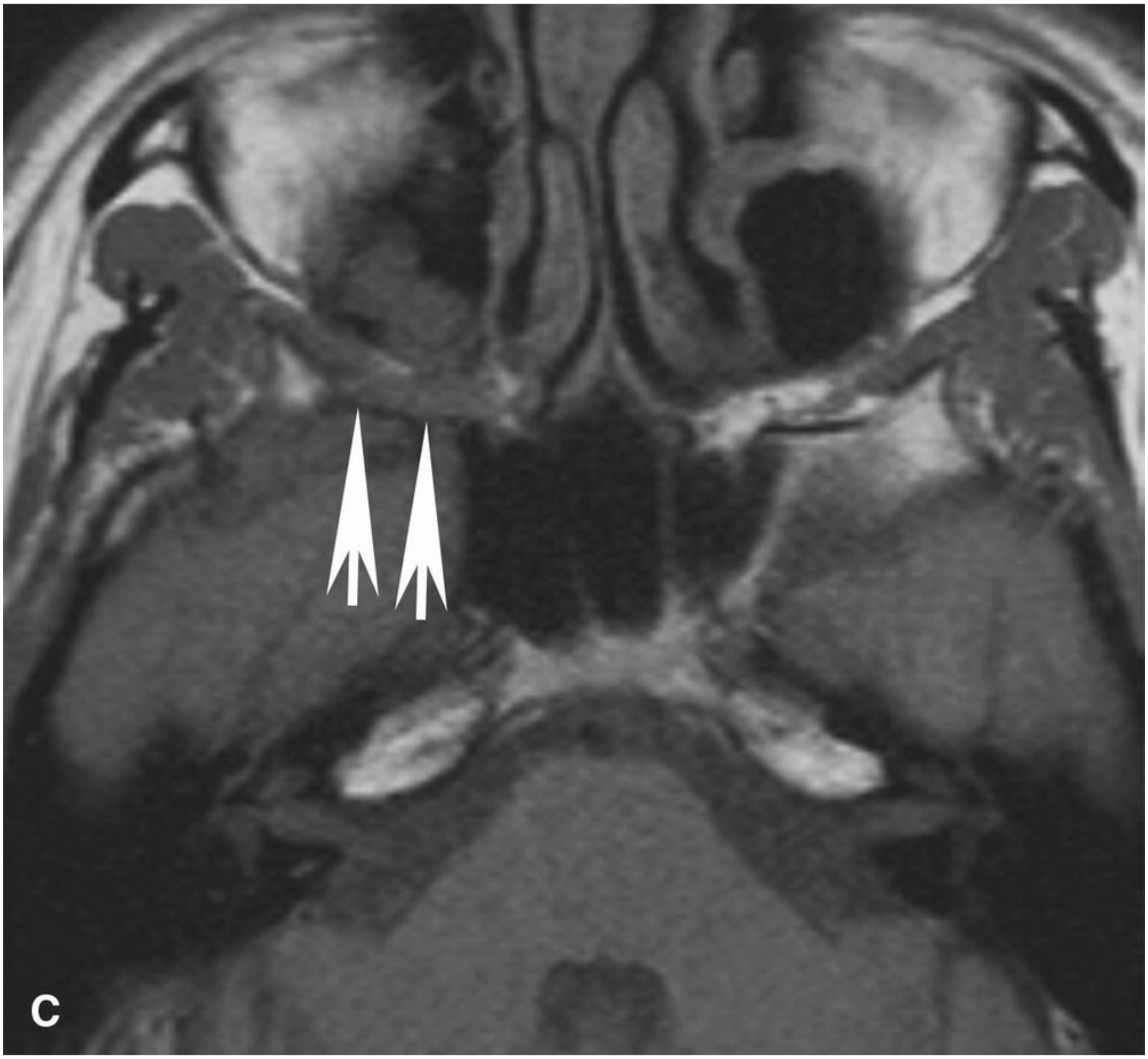
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Figure 5.22. Perineural spread (PNS) of tumor. Axial contrast-enhanced CT scan displayed in soft tissue **(A)** and bone windows **(B)** as well as unenhanced T1w **(C)** and contrast-enhanced fat-suppressed T1w **(D)** MRI images are shown from a patient with adenoid cystic carcinoma of the right maxillary sinus (primary not shown). On the CT, there is asymmetry with obliteration of normal fat in the right pterygopalatine fossa (PPF; **A**; *arrows*) and mild asymmetry with expansion and remodeling of its bony margins (**B**; *arrows*). On MRI, there is loss of the normal expected fat signal intensity (*arrows* in **C**) and abnormal enhancement (*arrows* in **D**).

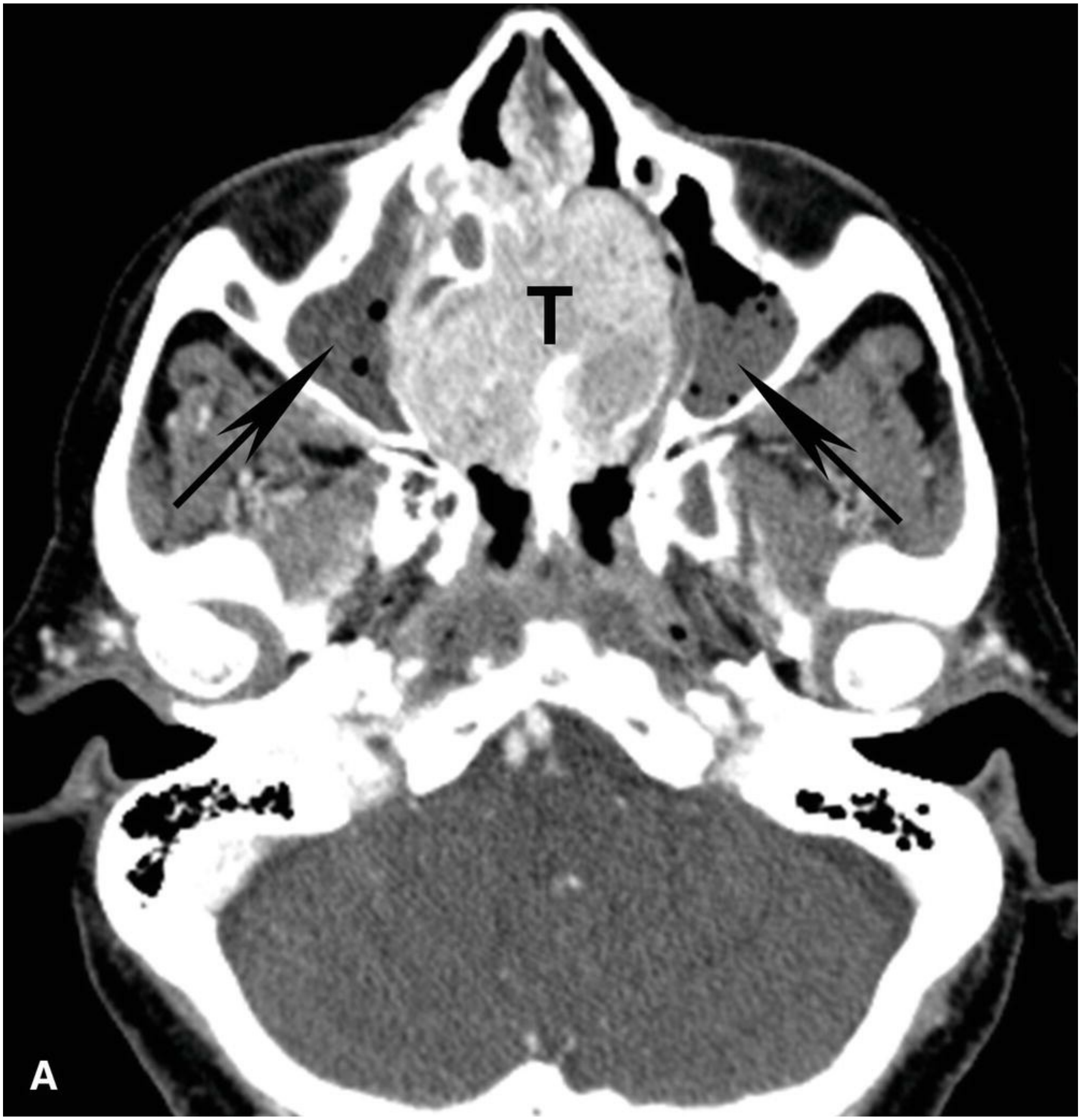
For evaluation of PNS, the MRI should be performed as a high-resolution exam with section thickness of no more than 3 mm through the skull base.[26]

Familiarity with detailed cranial nerve anatomy and patterns of spread is essential for optimal interpretation of these studies. Particular attention should be paid to key areas such as PPF, foramen ovale and rotundum, and the stylomastoid foramen. However, the spread pattern partly depends on the location of the primary tumor, requiring carefully directed assessment of neural pathways at risk. Attention should also be paid to indirect signs of PNS, such as denervation change (Fig. 5.8), as a clue to the presence of PNS.

SITE-SPECIFIC CONSIDERATIONS AND PATTERNS OF TUMOR SPREAD

Nasal Cavity and Paranasal Sinuses

Sinonasal malignancies are rare, constituting <5% of malignant head and neck neoplasms.[61–63] Malignancies involving the nasal cavity and paranasal sinuses are usually considered together, except for cancers of the nasal vestibule. SCC is the most common sinonasal cancer, followed by intestinal-type adenocarcinoma.[61,62] Other less common sinonasal cancers include adenoid cystic carcinoma, mucoepidermoid carcinoma, sinonasal undifferentiated carcinoma, melanoma, and olfactory neuroblastoma (Fig. 5.23). Rarely, other malignant neoplasms such as neuroendocrine carcinoma (Fig. 5.24), lymphomas (Fig. 5.25), sarcomas, and metastases from other primary sites, among other rare entities, may affect the paranasal sinuses.[62–64] In the paranasal sinuses, the maxillary sinus is most commonly affected. The ethmoids are less commonly affected, and the frontal and sphenoid sinuses are rarely affected.[61,62]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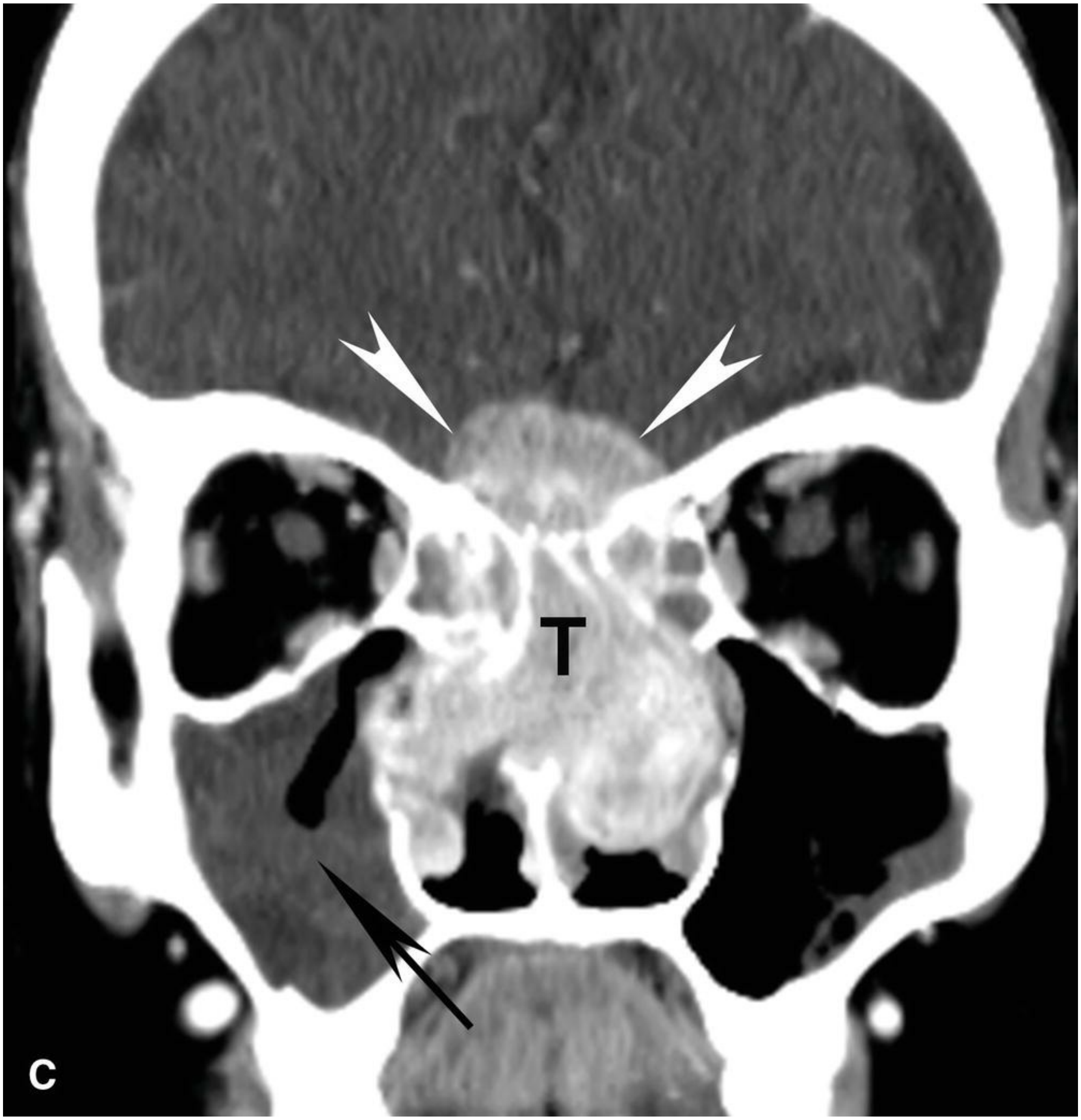
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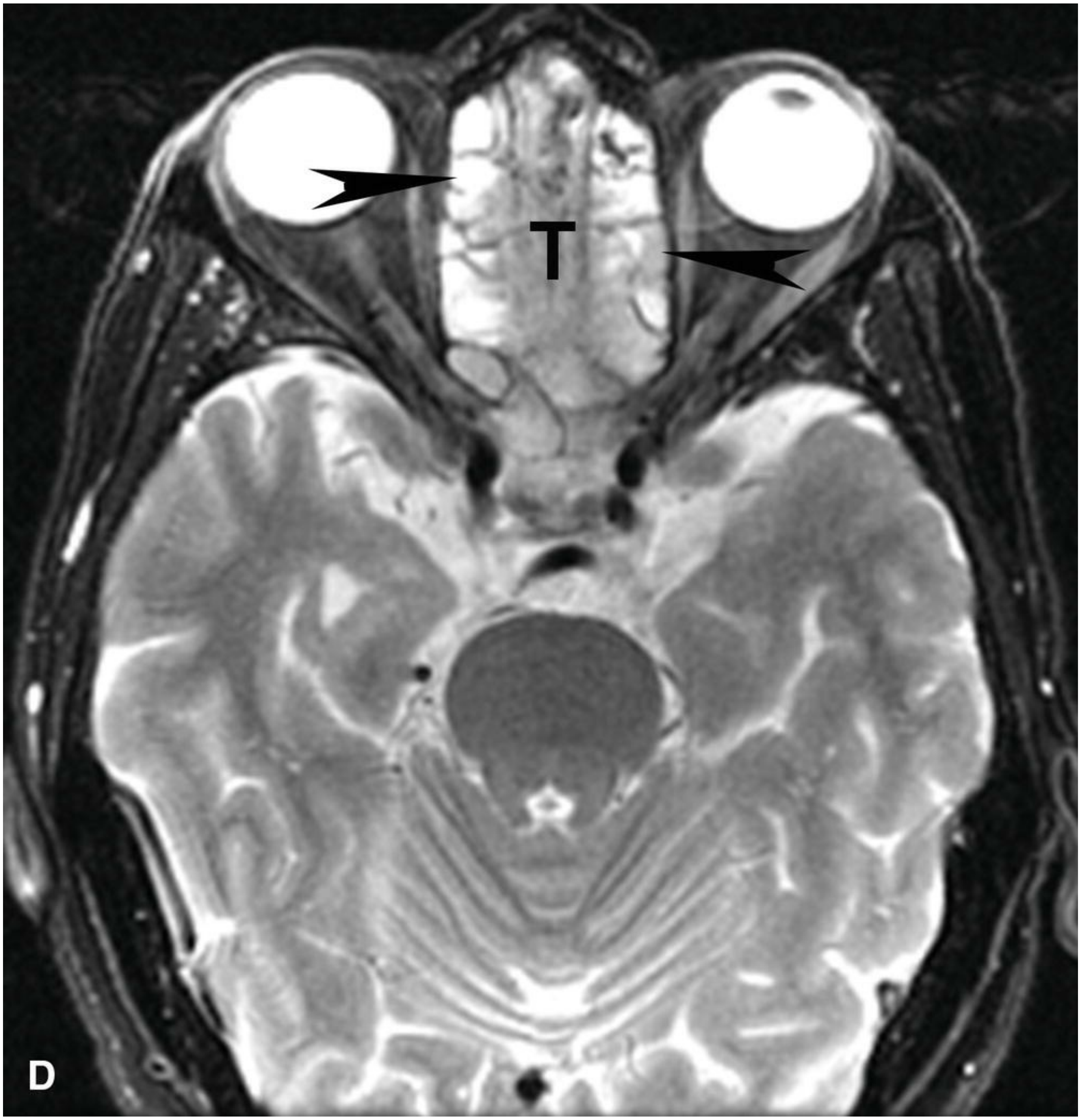
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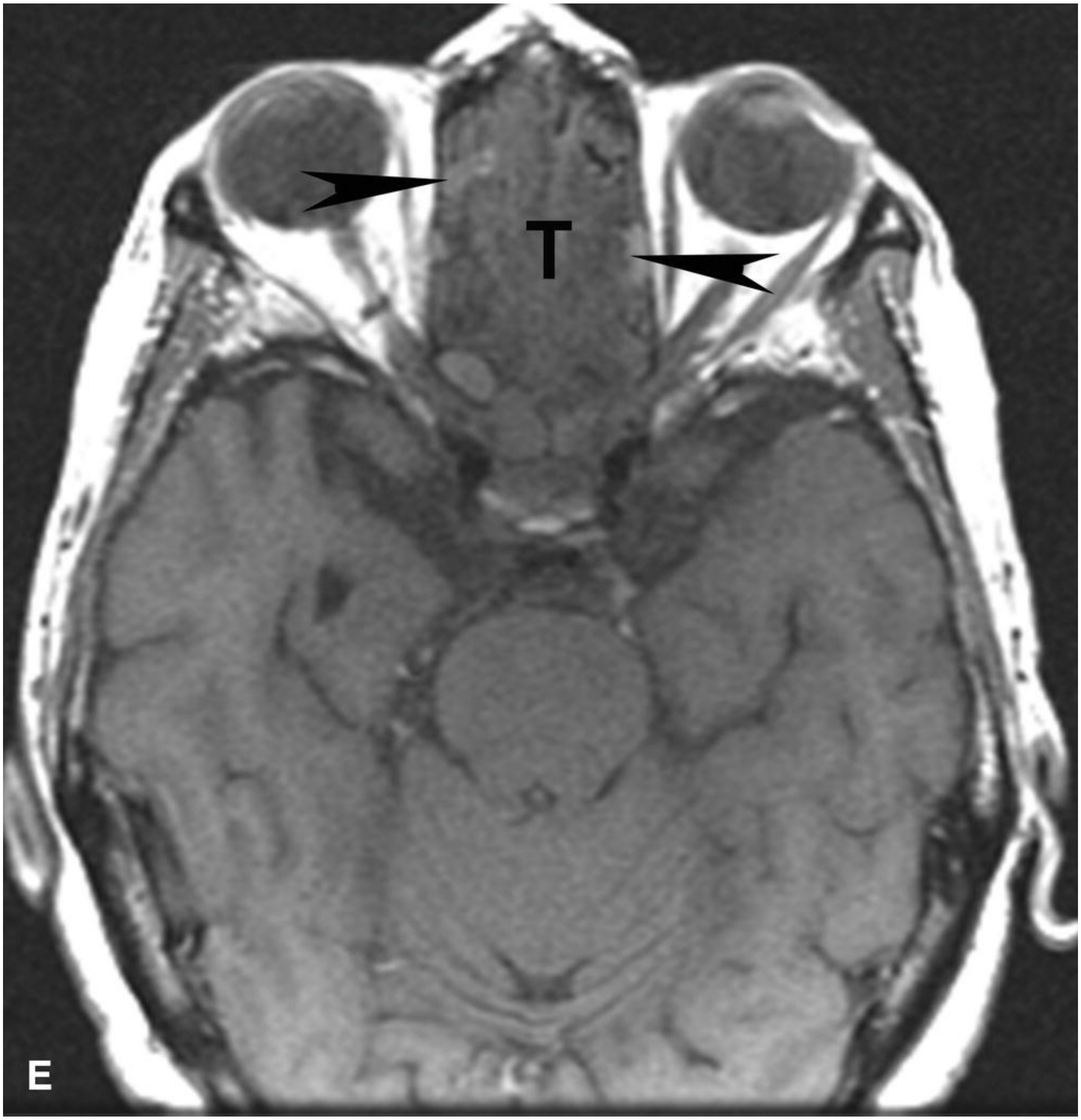

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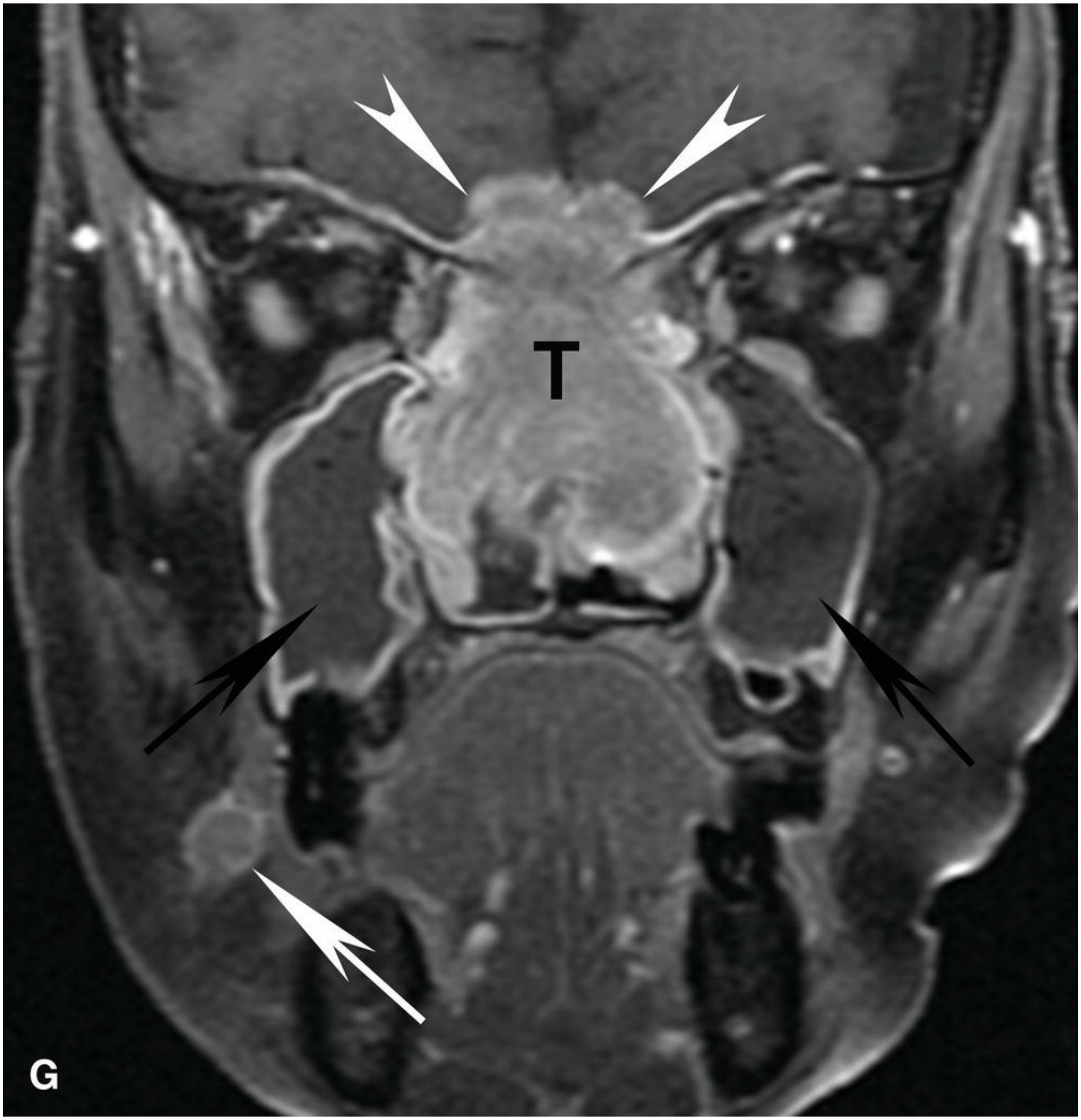
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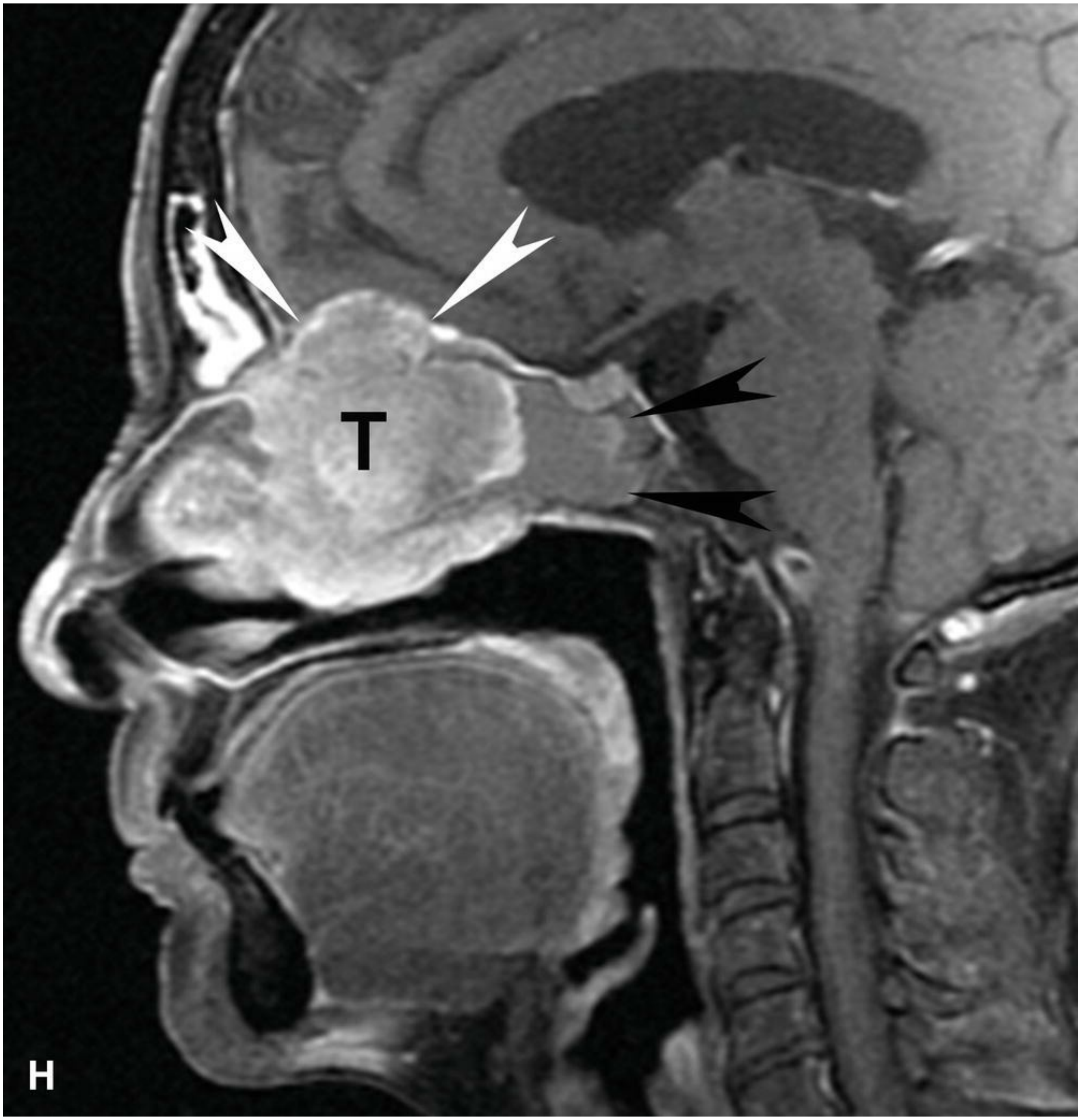
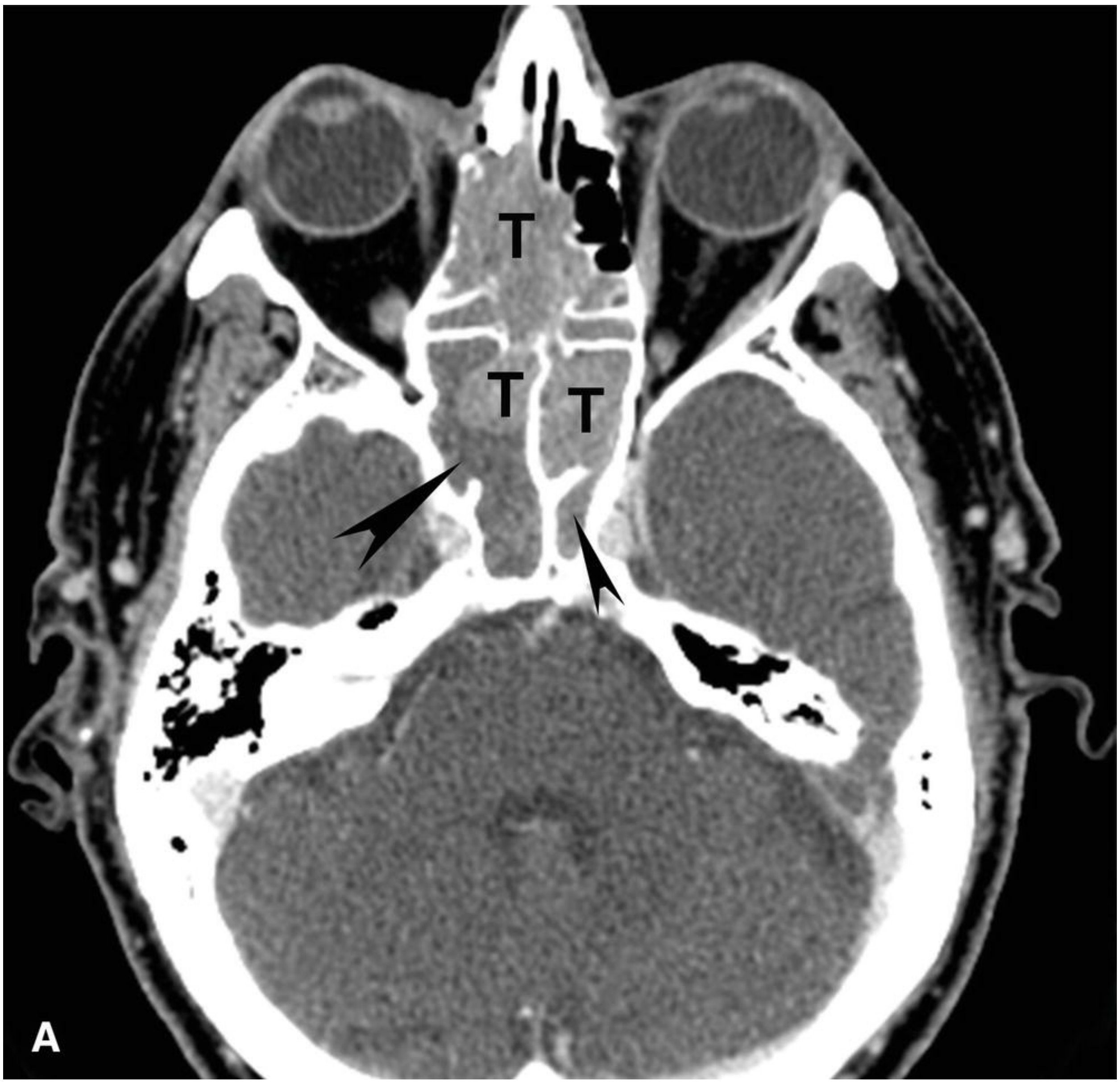
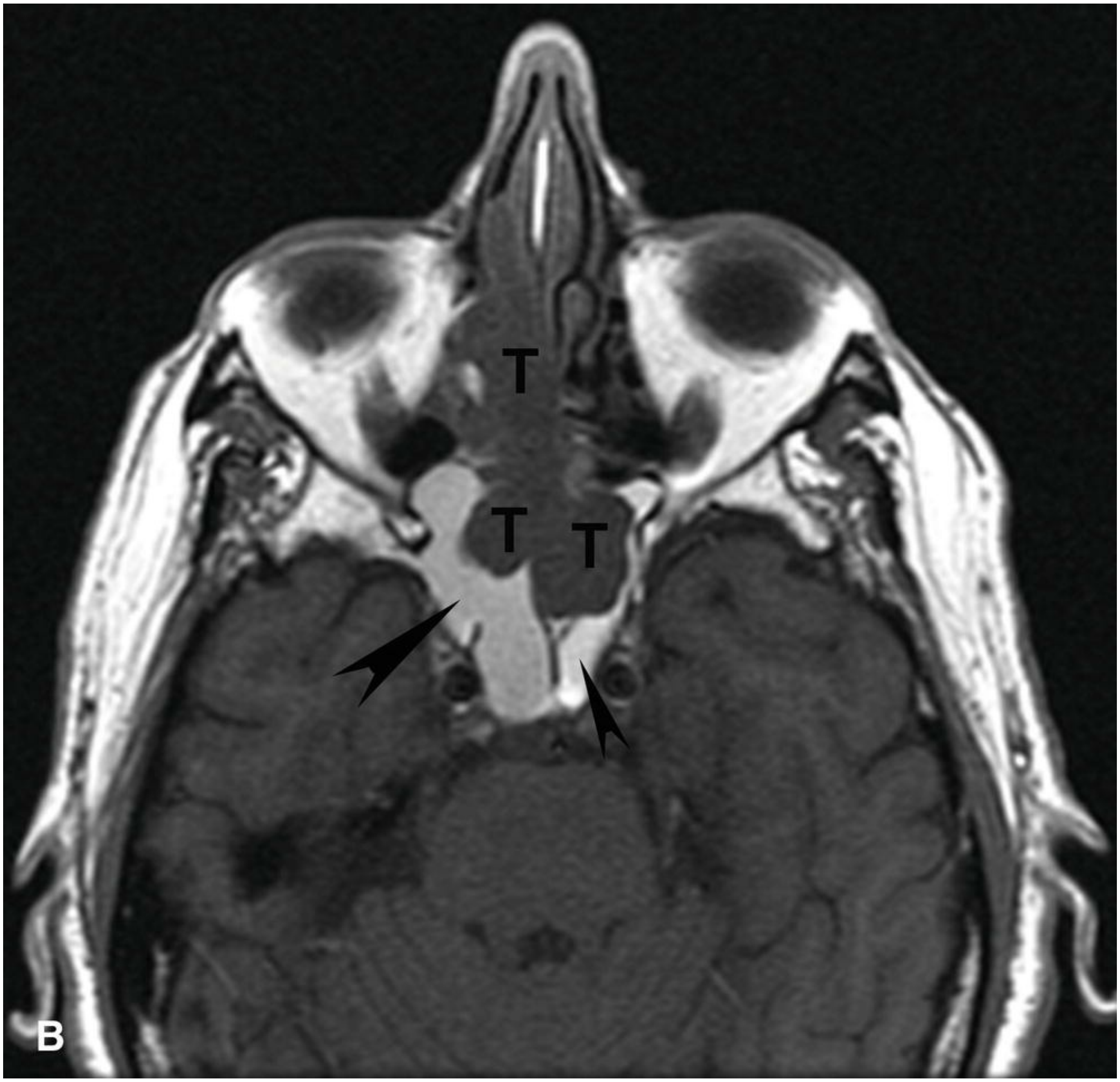


Figure 5.23. Olfactory neuroblastoma (ONB) with intracranial spread and facial node metastasis. Axial and coronal reformatted contrast-enhanced CT **(A–C)**, axial T2w **(D)**, T1w **(E)**, and contrast-enhanced T1FS **(F–H)** MRI images are shown. The tumor has a wide base with intracranial spread, which may be used to suggest ONB as a differential consideration, but the appearance and signal are otherwise nonspecific and biopsy is required for diagnosis (also compare to Figs. 5.24 and 5.25). In this case, the enhancing tumor (T) is clearly distinguishable from relatively low-density secretions in the maxillary sinuses (*black arrows* in **A and C**) and the signal of secretions

on MRI (*black arrowheads*). The *black arrowheads* point to secretions in some ethmoid air cells **(D–G)** and in the sphenoid sinus **(H)**. Note the variations in signal of the secretions adjacent to the mass, some with higher signal on T1w **(E)** suggestive of higher protein content. As expected, the secretions mostly have higher signal than tumor on T2w **(D)**. However, combined evaluation of all sequences clearly distinguishes tumor from the secretions, especially on the contrast-enhanced MRI images in most areas. The *white arrowheads* indicate intracranial extension of tumor. *White arrow* points to the right facial node metastasis **(B,G)**.

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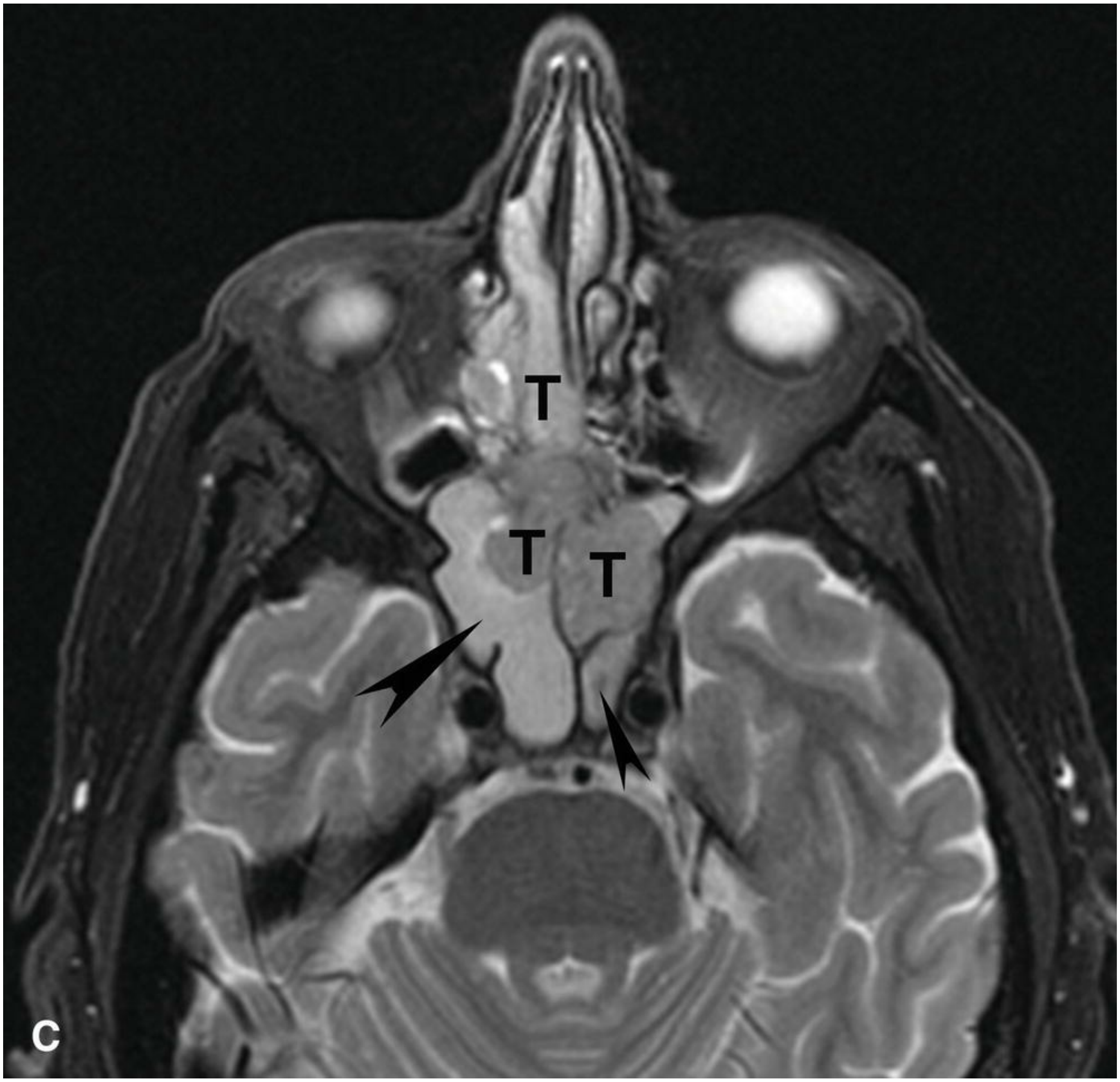
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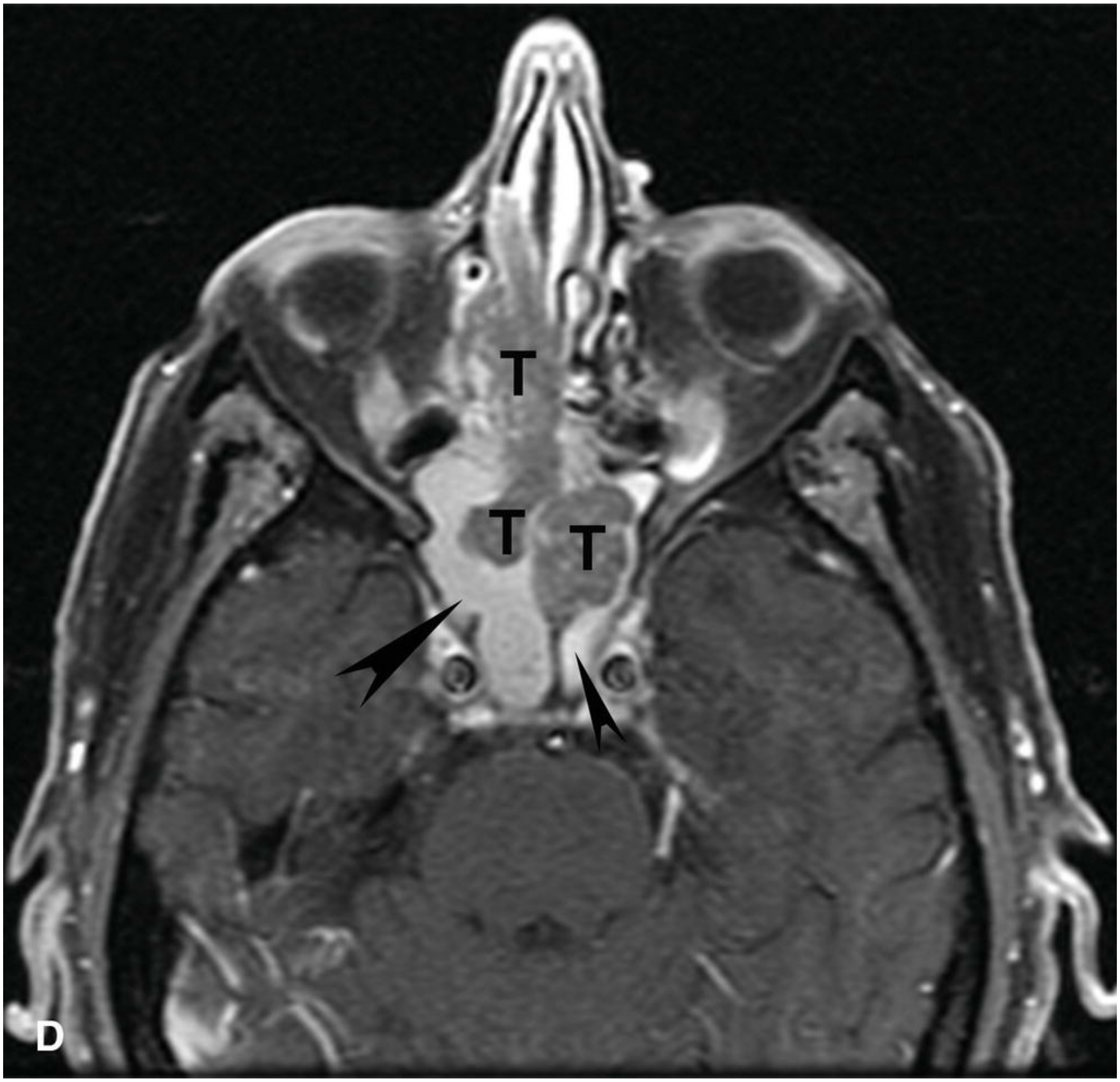
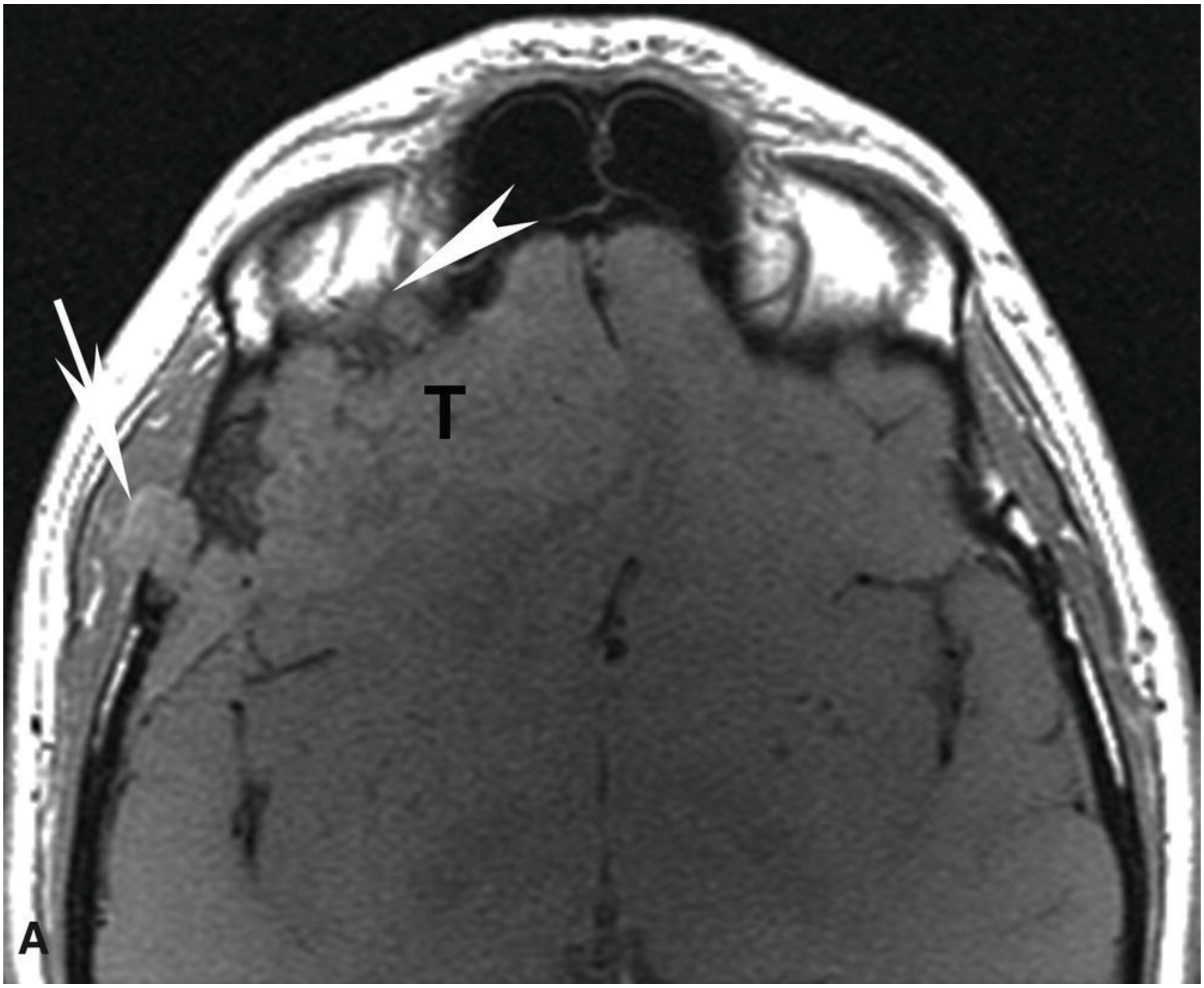


Figure 5.24. High-grade neuroendocrine sinonasal carcinoma: Differences in signal obstructive secretions. Axial contrast-enhanced CT **(A)** and axial T1w **(B)**, fat-suppressed T2w **(C)**, and contrast-enhanced fat-suppressed T1w **(D)** MRI images are shown from a 76-year-old male patient. On CT, parts of the tumor (T) have very similar density to the obstructive secretions and thus difficult to distinguish from tumor, especially in the left sphenoid sinus (*small arrowhead*). On MRI, on the other hand, the secretions are clearly distinguishable from tumor signal. Note that the higher density proteinaceous secretions in the left sphenoid sinus on CT also have lower signal on T2w and higher signal on T1w (*small arrowheads*) compared to the more watery secretions in the right sphenoid sinus (*large arrowhead*; see text for

explanations).

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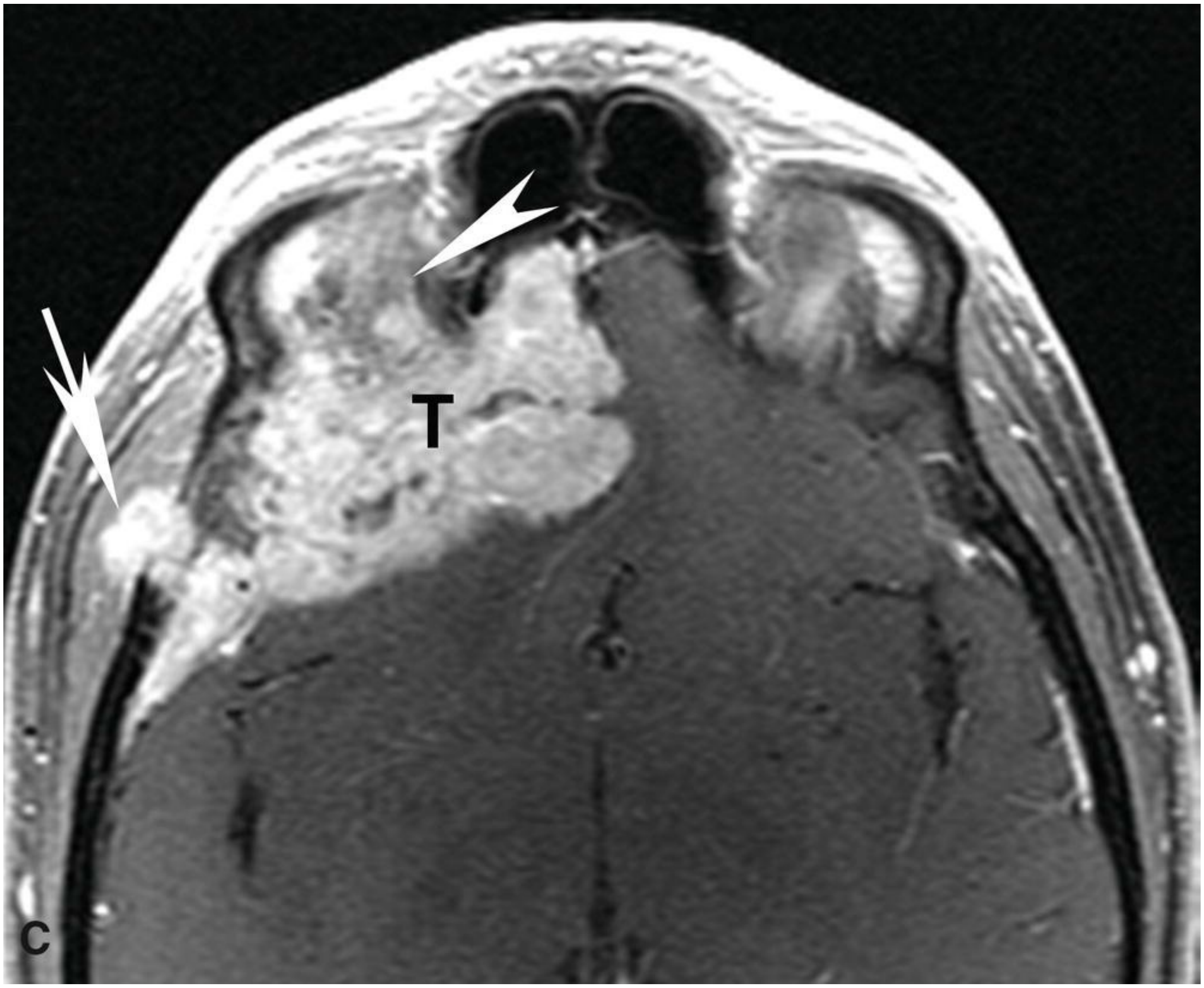
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Figure 5.25. Anterior skull base diffuse large B-cell lymphoma. T1w **(A)**, T2w **(B)**, and contrast-enhanced fat-suppressed T1w **(C, D)** MRI images are shown from a 37-year-old male patient. The large heterogeneously enhancing tumor (T) involves the anterior skull base with a large intracranial component, extends into the orbit with involvement of the orbital apex (*white arrowheads*), invades the right temporalis muscle (*white arrows*), and has a small component extending into the ethmoids. Note the cerebral edema at the site of compression on the T2w images (**B**, *black arrowheads*).

The main role of imaging in evaluation of sinonasal tumors is to accurately determine the lesion stage in order to guide therapy and surgical planning. Occasionally, imaging can help narrow the differential for sinonasal tumors, but preoperative differentiation of different histologic subtypes of tumors is often not possible (Figs. 5.23 to 5.25), perhaps with the exception of melanotic melanomas, which may appear hyperintense to gray

matter on unenhanced T1w images.[63] Regardless, a biopsy is required for a histopathologic diagnosis.

Sinonasal cancers typically spread by direct and perineural extension[63] and frequently present with a relatively advanced stage (Fig. 5.23). Because of their proximity to multiple critical structures, it is important to carefully evaluate extension outside the sinonasal region[65] (Figs. 5.23 and 5.25). Specific evaluation needs to be made for invasion of the orbits or intracranial compartment, including specific assessment of orbital apex involvement. Invasion of clivus/skull base changes the stage and should be noted.

As mentioned, sinonasal tumors can also spread by perineural extension. The major nerves supplying the sinonasal region are the first two divisions of the trigeminal nerve. The second branch (maxillary division) of the trigeminal nerve is most likely to be involved. The PPF represents the site of convergence of multiple neural pathways and must be specifically evaluated on every scan. Spread of tumor to the PPF can provide a route for further spread into the orbit, intracranial compartment, infratemporal fossa, skull base, and even the oral cavity.[65]

Lymph node metastases from sinonasal cancers are relatively uncommon[63] (Fig. 5.23). However, when present, they usually indicate tumor spread outside of the sinonasal cavity and portend a poor prognosis. Nodal metastases are most commonly seen with tumors of the maxillary antrum. The lateral retropharyngeal nodes represent the primary nodal drainage area for these tumors. However, the lymphatic drainage is inconstant and variable, and as result, the upper internal jugular and level IB nodes are the most common sites harboring nodal metastases.[63] The site of metastasis partly depends on the location of the tumor.

CT and MRI are complementary for evaluation of sinonasal tumors. CT is excellent for evaluating bone detail and demonstrates the tumor–air interface very well (Figs. 5.23 and 5.24). CT also provides the necessary landmarks for sinonasal and skull base surgery. Inflammatory changes and secretions within the sinus, such as secondary to outflow obstruction from tumor, on the other hand, can sometimes have similar attenuation to tumor (Fig. 5.24). Secretions with low protein content have a low density and typically can be distinguished from intermediate to high soft tissue density of tumor (Fig. 5.23). However, higher density secretions and/or lower density

tumors may be indistinguishable on CT (Fig. 5.24). After administration of contrast, most tumors enhance whereas secretions do not have solid enhancement (Figs. 5.23 and 5.24).

Whereas CT is excellent for demonstrating bone detail, MRI is generally considered superior for determination of overall extent of tumor (Figs. 5.23 to 5.25). MRI is especially superior to CT for detection of the extent of tumor spread outside the paranasal sinuses, such as in the intracranial compartment, for evaluation of PNS, and for distinction of tumor from inflammatory and postobstructive changes and secretions (Figs. 5.23 to 5.25). Like on CT, the appearance of secretions on MRI depends on their protein content. Watery, low protein content secretions have fluid signal that is hypointense on T1w and hyperintense on T2w[65] (Figs. 5.23 and 5.24). Particularly with chronic obstruction, protein concentration of secretions tends to increase (Fig. 5.24). Typically, this results in increased signal on T1 (Fig. 5.24). The signal of secretions initially remains high on T2, but starting at ~25% protein content, the signal starts to drop on T2w images as well (Fig. 5.24). With very high protein content, typically >28%, the signal of secretions will decrease on both T1 and T2w images. If the protein content is high enough, the secretions can occasionally present as a signal void on both sequences and mimic a normal aerated sinus on MRI.[65] Regardless of signal variations, secretions are almost always distinguishable from soft tissue signal and solid enhancement of tumor. The normal linear mucosal enhancement should not be mistaken for tumor (Fig. 5.23). MRI is more sensitive for detection of bone marrow infiltration. Multiplanar assessment, and particularly coronal images, are essential for the evaluation of the roof of the ethmoid, cribriform plate, orbital roofs, floor of anterior cranial fossa, and palate and should be performed both on CT and MRI.[65]

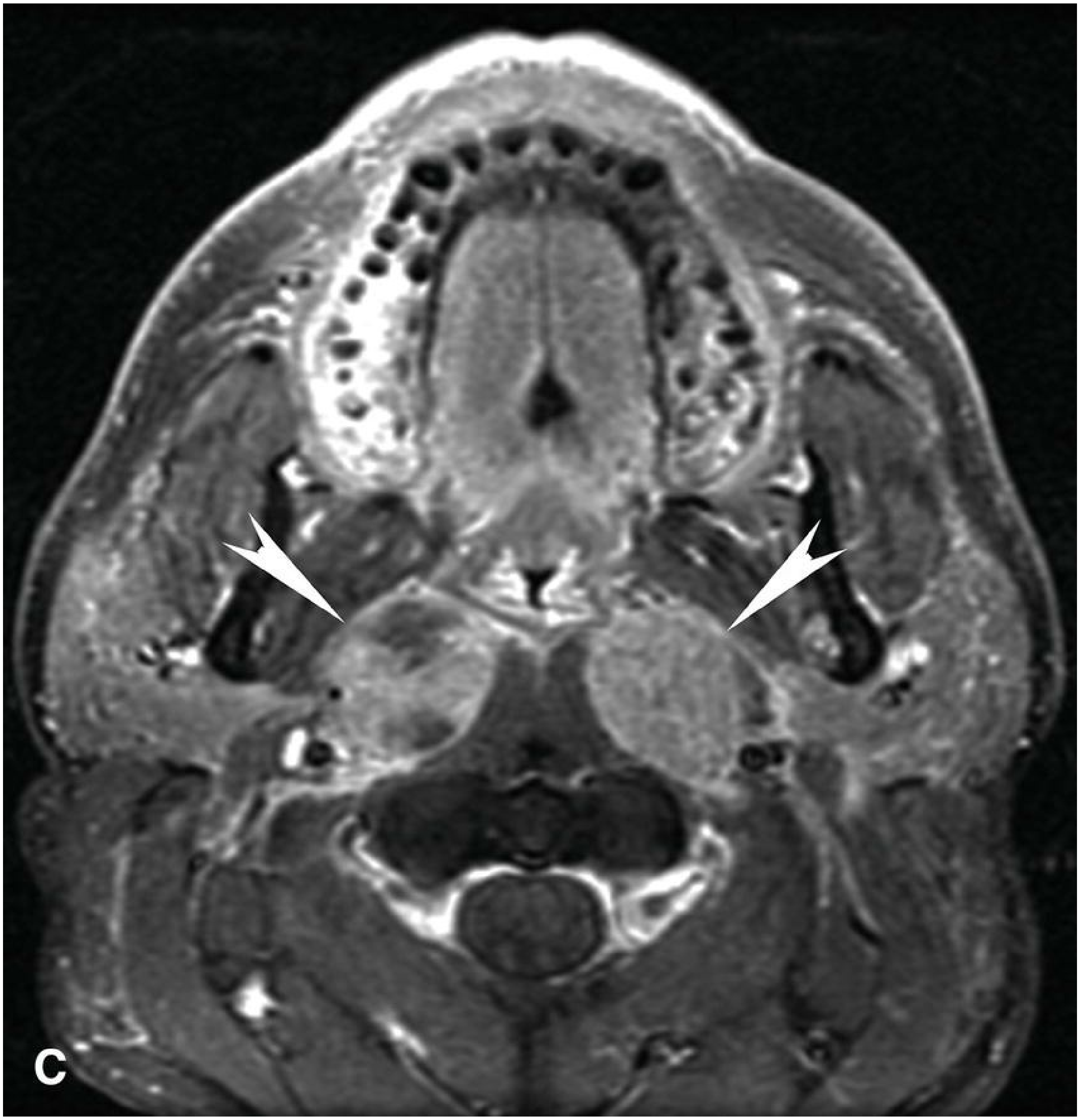
Nasopharynx

NPC is a distinct disease from SCC. NPC has the highest incidence in Southeast Asia but is less common in the West and among Caucasians[66] and, according to the WHO classification, has 3 histologic subtypes. In general, NPC is a locally aggressive neoplasm with a high propensity for nodal spread (Figs. 5.26 and 5.27). Uncommonly, other tumor types may arise in the nasopharynx (Fig. 5.21). Although NPC may arise at any site in the nasopharynx, it frequently arises in the region of the fossa of Rosenmüller[67]

(Fig. 5.27). The nasopharyngeal mucosa is surrounded by a muscular and fascial sling constituted by the superior constrictor muscles and the buccopharyngeal fascia, derived from the middle layer of deep cervical fascia.[66] There is also the pharyngobasilar fascia (PBF), a tough aponeurosis extending from the superior constrictor muscles to the skull base. However, there are defects in the PBF on either side at the site of passage of the eustachian tube and levator veli palatini muscle, referred to as the sinus of Morgagni. The PBF can be seen on T2w images as thin low intensity line extending posteriorly from the medial pterygoid plates and lining the lateral and posterior nasopharyngeal walls.[66] NPC may spread submucosally or transgress adjacent fascial boundaries or defect and invade adjacent spaces such as the masticator and retropharyngeal spaces.[67,68] Invasion of the skull base may occur directly adjacent to the tumor site or tumor may spread via foramen lacerum and the neural foramina along the floor of the middle cranial fossa.[67] Extension along the course of the Eustachian tube potentially provides access to the middle ear, but this is very rare. Extension into adjacent spaces, including the parapharyngeal space, skull base, paranasal sinuses, intracranial compartment, masticator space, or beyond needs to be documented when present for proper staging. PNS of tumor primarily occurs after tumor has invaded into the PPF, or foramen ovale, and may thus facilitate intracranial spread and is a T4 designator.[67]


A


B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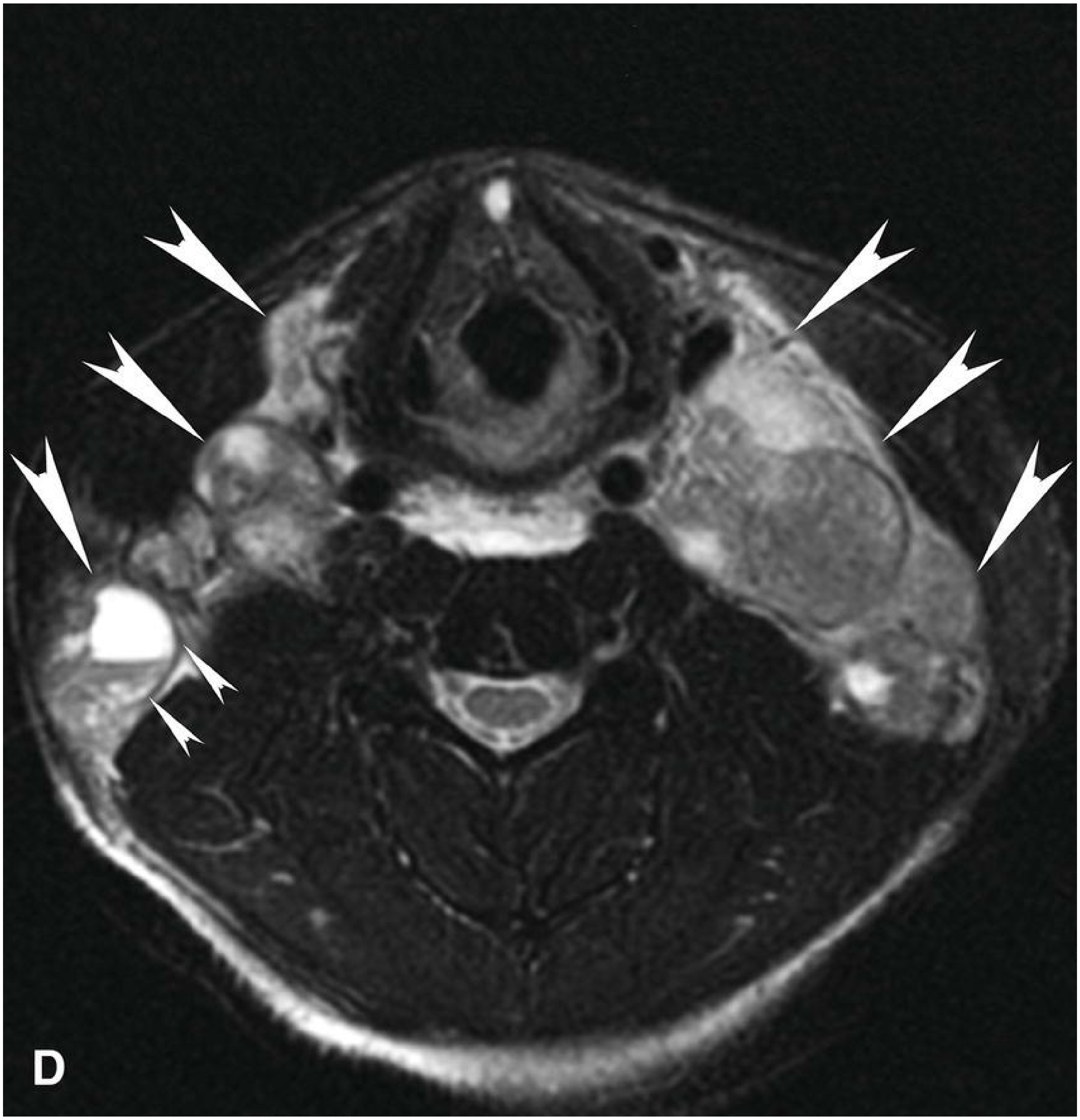
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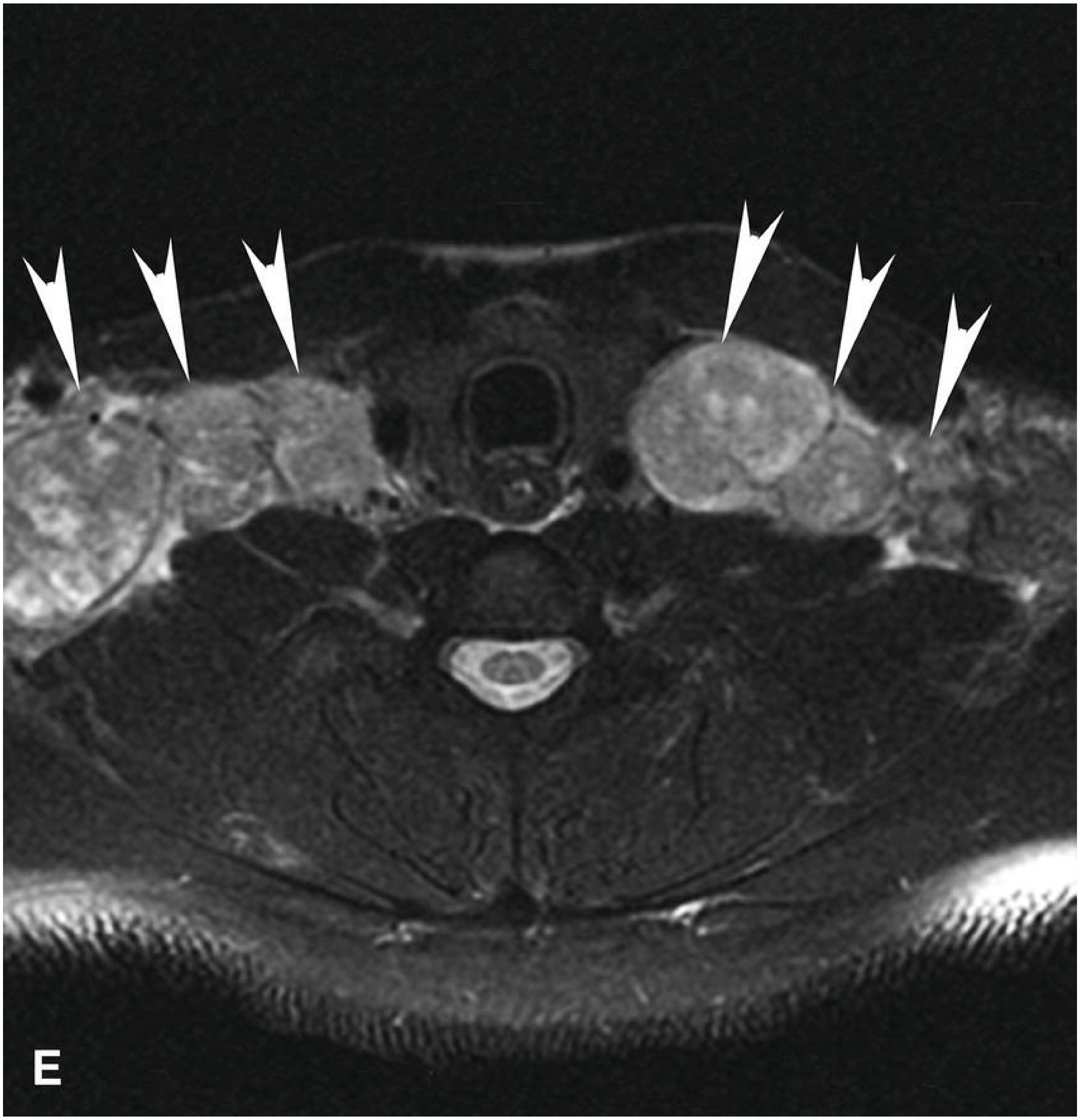
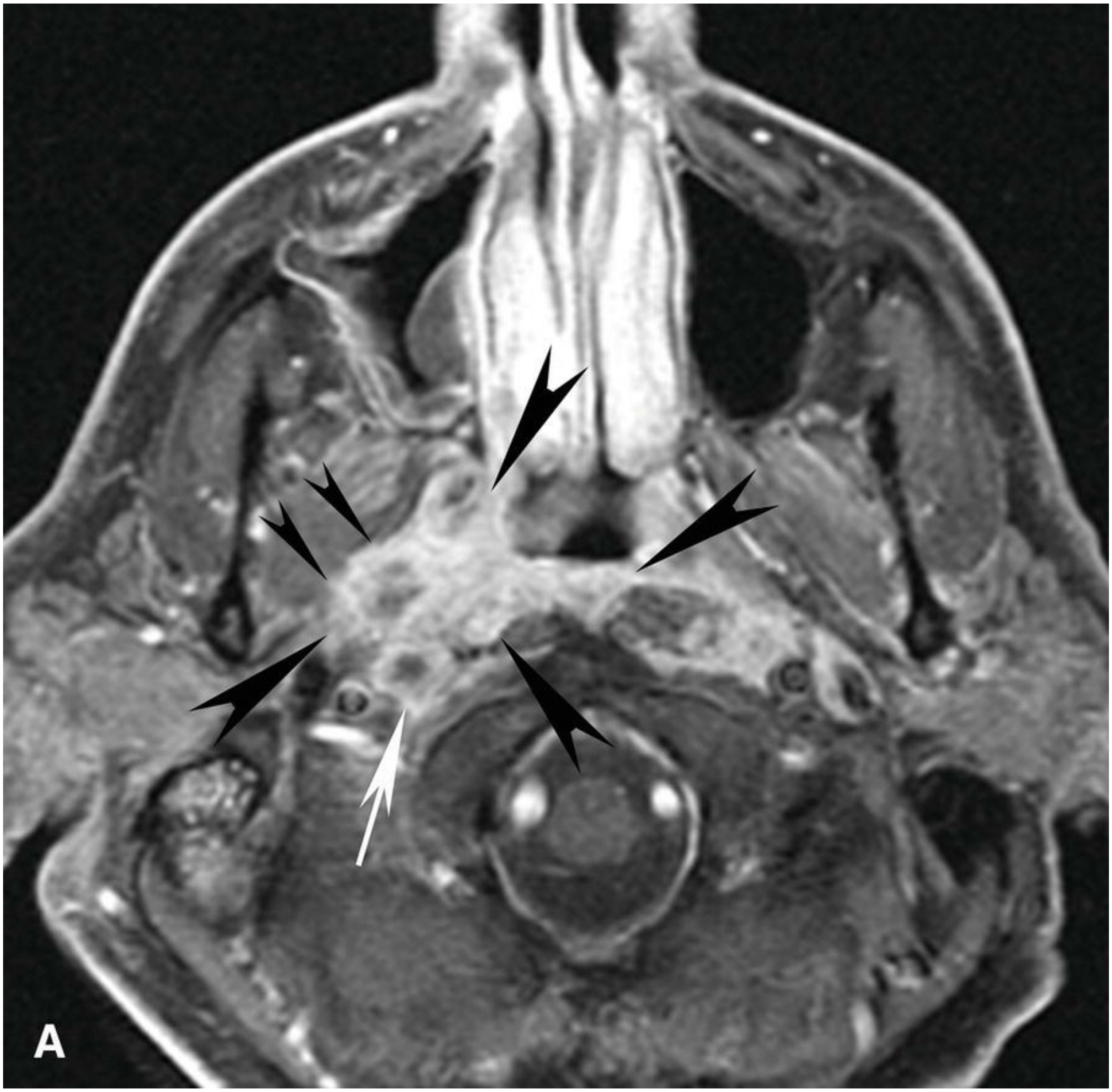
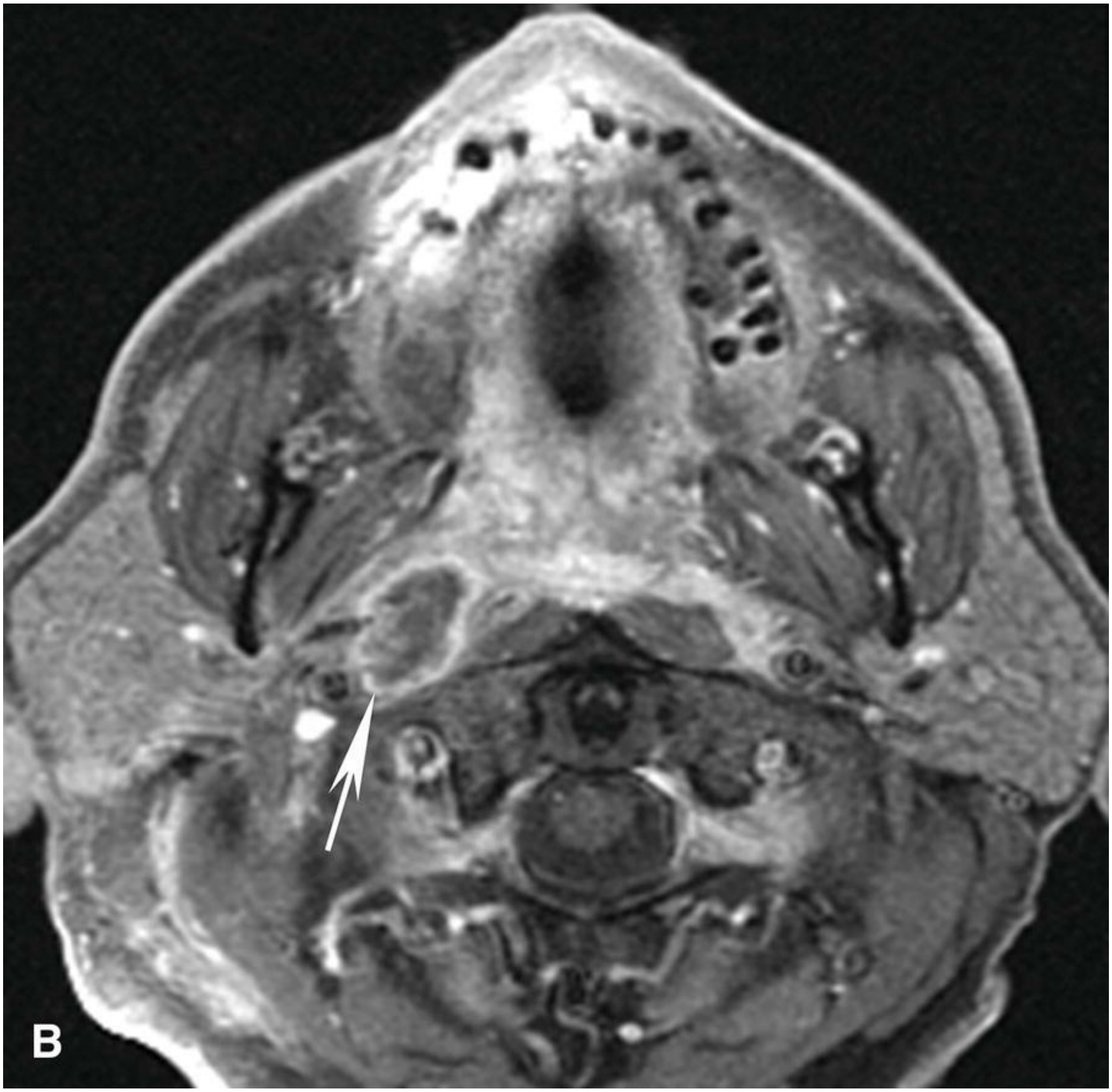


Figure 5.26. Nasopharyngeal carcinoma (NPC). Axial T2FS **(A, B, D, E)** and axial contrast-enhanced fat-suppressed T1w **(C)** MRI images are shown from a 39-year-old man presenting with NPC. The primary mass (**A**; *arrows*) is relatively noninvasive, T2 stage. However, there is massive bilateral cervical lymphadenopathy (**B–E**; *large arrowheads*) including the lateral retropharyngeal nodes **(B, C)**, level II (not shown), level III **(D)**, level IV **(E)**, and level V **(E)**. This is a good example highlighting the propensity of this tumor for nodal spread, presenting with N3 stage. Note the fluid level in the right level VA node (**D**; *small double arrowheads*), a rare presentation of

necrosis. There are also typical inhomogeneous/necrotic nodes elsewhere, including the retropharyngeal nodes (*arrowheads*, **B, C**).

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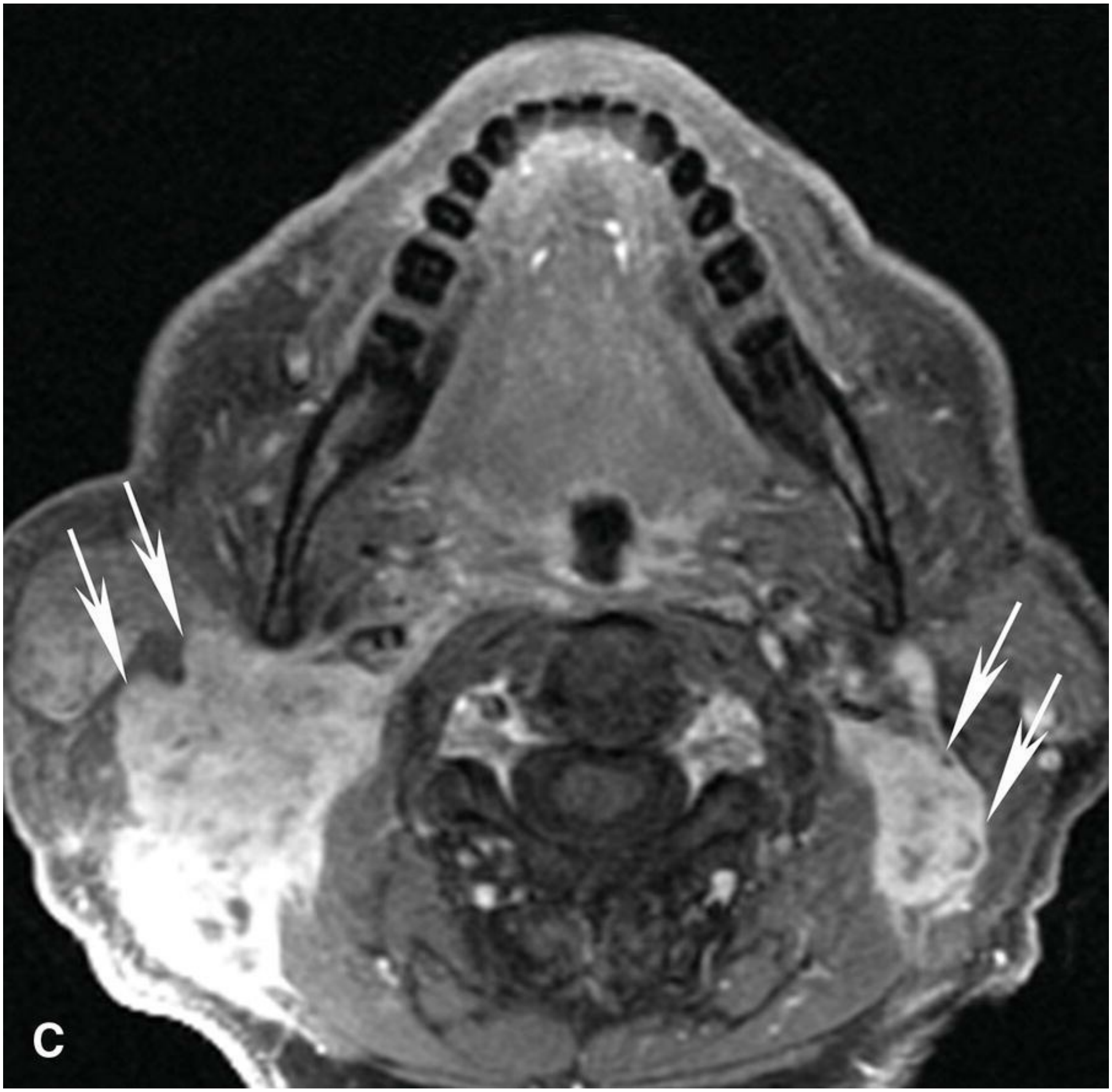


Figure 5.27. Nasopharyngeal carcinoma (NPC). **A–C:**Axial contrast-enhanced T1FS MRI images are shown from a 73-year-old man presenting with NPC (**A**; *large black arrowheads*). The lesion is centered in the region of the right fossa of Rosenmüller, the most common site of origin of NPC. There is submucosal spread of tumor along with invasion of the right longus muscles. In addition, there is a small area of focal spread across the right parapharyngeal space into the right masticator space (*small black arrowheads*). There is extensive lymphadenopathy including a necrotic right lateral retropharyngeal node (**A, B**; *white arrow*) and bilateral conglomerate level II adenopathy (**C**; *double white arrows*).

The appearance of NPC, particularly when small, is nonspecific on imaging and can overlap with normal adenoid tissues. Laterality and presence of excess tissue in the region of fossa of Rosenmüller should heighten suspicion for presence of tumor and trigger endoscopic evaluation, particularly in a patient presenting with middle ear effusion or other clinical signs suggesting possible NPC. Although both CT and MRI play a role in evaluation of NPC, MRI has been demonstrated to be superior for initial T stage determination of biopsy-proven NPC.[1–6] On MRI, NPC usually is typically isointense relative to muscle signal on T1w images and relatively hypointense on T2w images (although still hyperintense with respect to muscle). After contrast administration, there is moderate to intense enhancement of the tumor (Fig. 5.27).

When evaluating the nasopharynx, especial attention needs to be made to any asymmetry in tissues and obliteration of fat planes. Similar to other sites, when evaluating for bone invasion, attention needs to be paid to tumor signal within the bone to try and distinguish marrow edema. In addition to axial images, coronal and sagittal images can be very useful for evaluation of roof of nasopharynx and bone invasion. Evaluation of cavernous sinuses, intracranial compartment, and PNS is best done with MRI. In the AJCC classification, the N staging of NPC is different from other head and neck cancers. NPC has high propensity for nodal spread, and there are frequently nodal metastases at the time of presentation, in 60% to 90% of cases[66] (Figs. 5.26 and 5.27). The most common sites of nodal spread from NPC are to levels II, III, IV, and V, the lateral retropharyngeal nodes, and the posterior auricular nodes.[46,69]

Oral Cavity

Cancers of the oral cavity are considered separately from those of the oropharynx because malignancies such as SCC of the oral cavity tend to differ from those arising in the oropharynx in presentation, routes of spread, and clinical management. A large and varied collection of benign and malignant tumors may arise in the oral cavity, but among the malignancies, >90% are SCC.[70] The oral cavity has multiple anatomic subsites that include the lip (mucosal part), buccal mucosa, floor of mouth (FOM), oral tongue, retromolar trigone (RMT; or retromolar gingiva), hard palate, and alveolar ridge. The alveolar ridge may be further divided into upper and lower

alveolar ridge, referring to the mucosa overlying the alveolar process of the maxilla and mandible, respectively. Two of the most common oral cavity cancers are those arising in the oral tongue (Figs. 5.3 and 5.6) and FOM (Fig. 5.28). The nodal spread patterns of SCCs of the oral cavity partly depend on the specific subsite, but overall, the most common nodal groups involved are levels I, II, and III.

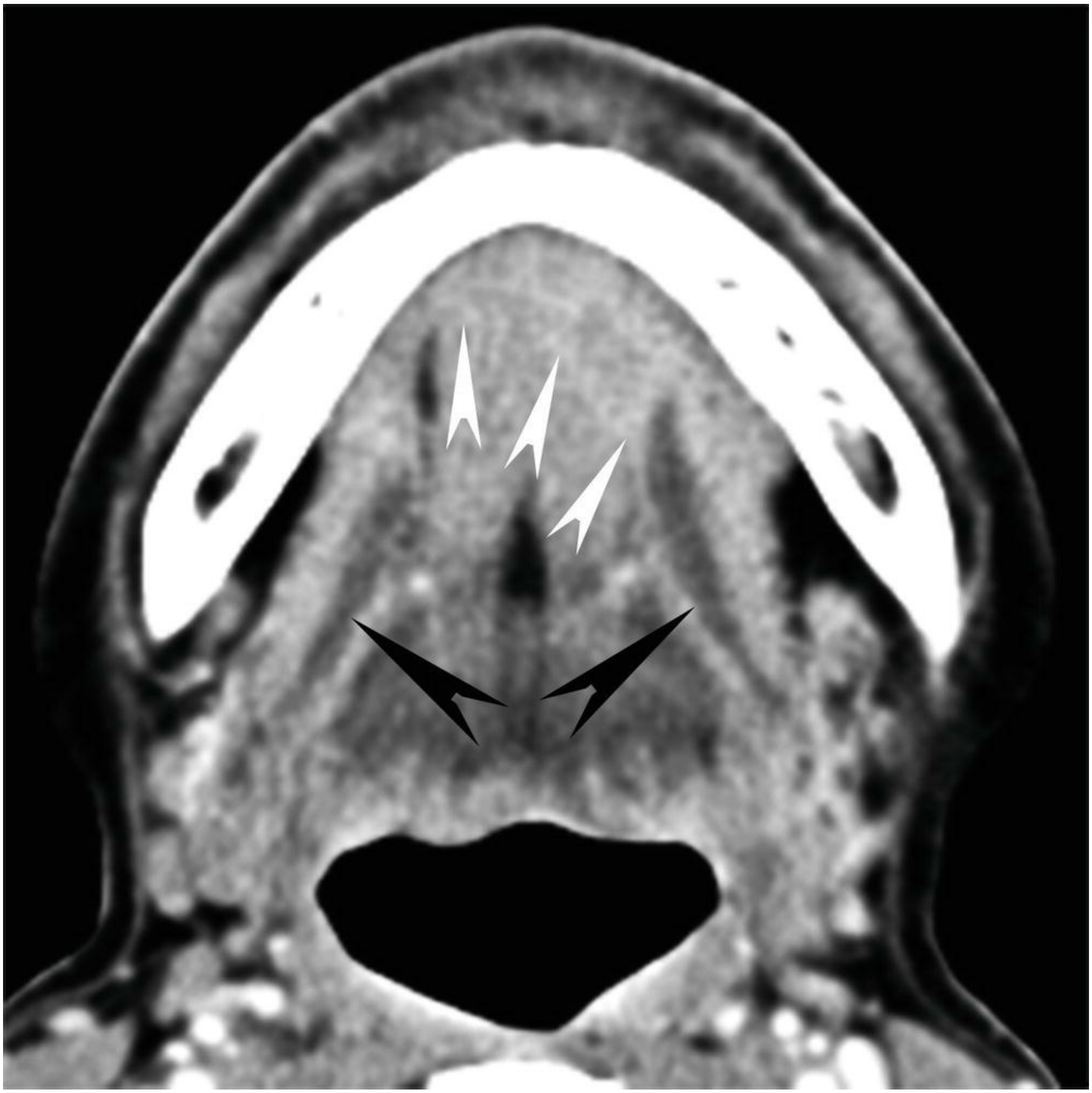


Figure 5.28. Floor of mouth (FOM) SCC. Axial contrast-enhanced CT demonstrates a very subtle lesion in the anterior left FOM (*small white arrowheads*), crossing to the contralateral sublingual space (SLS). The tumor

can barely be distinguished from adjacent normal soft tissues. One clue is the asymmetry in the left SLS. A more obvious clue is the presence of bilateral Wharton duct obstruction (*large black arrowheads*) by the tumor.

The CT and MRI appearance of oral cavity SCC is similar to other sites and was described earlier. MRI has been reported to have a slight advantage for evaluation of tumors, especially determination of T stage, tends to be less prone to dental artifact, and may improve visualization of the lesion at some subsites such as the hard palate (Fig. 5.5) and FOM.[37,71–74] Frequently, CT is still used as the first-line modality for evaluation of oral cavity cancer, and an MRI can be obtained to complement the evaluation for specific indications. These include evaluation of equivocal lesions or lesions obscured by dental artifact, hard palate lesions because these can be understaged on CT, complementary evaluation of bone to assess for marrow invasion, and for evaluation of PNS. As discussed earlier, the technologists should be trained to automatically perform a second acquisition covering the oral cavity and oropharynx at a different angle whenever they identify dental work on the scout view used for acquisition planning. This will increase the yield of the scan and can uncover pathology that would otherwise be obscured by dental artifact. For lesions affecting the oral tongue, obtaining an additional acquisition with the tongue out can also be helpful and may reveal an otherwise obscured lesion out of region of severe dental artifact.

Oral tongue SCC occurs on the lateral and ventral (undersurface) aspect of the tongue, in its middle and posterior thirds[70] (Fig. 5.6). These tumors may spread medially into the tongue musculature (Figs. 5.3 and 5.6) or spread along the extrinsic muscles toward their sites of attachment outside the tongue such as mandible, hyoid bone, or styloid process. Tumors may also spread to the FOM, and posteriorly located tumors may spread to the base of the tongue (BOT) (Fig. 5.3). When advanced, these tumors may invade the mandible and this will be discussed in greater detail later. Sometimes, tumors may also spread superficially along the palatoglossus arch/anterior tonsillar pillar to the palate superiorly and posteriorly to the peritonsillar tissues. In evaluating these tumors, it is important to identify any extension across the midline into the contralateral tongue because this can significantly impact prognosis and management.[70,75] Invasion of neurovascular bundle and depth of invasion of tumor are also important to assess. Tumor thickness is an

independent prognostic factor for oral tongue cancers and should be reported. It is noteworthy that the fat content of the normal tongue can vary among individuals, and this can affect visibility of the lesion (Fig. 5.6).

SCCs of the FOM frequently arise near the anterior midline of the FOM (Fig. 5.28). The muscles of the FOM form a relative barrier to tumor spread, and therefore, these tumors tend to spread either horizontally or superiorly. Because of the proximity to the mandible, these tumors can directly invade the mandible. FOM tumors can also invade the neurovascular bundle and intrinsic tongue muscles. Because the sublingual spaces communicate anteriorly, this provides a route for contralateral extension as well (Fig. 5.28). FOM lesions can be subtle on CT due to isodensity with adjacent uninvolved tissue. Careful attention should be paid to obliteration of fat planes and asymmetry of the sublingual spaces (Fig. 5.28). Indirect signs, such as Wharton duct dilation secondary to obstruction of their ostia, can be helpful and be the only clue to the presence of tumor (Fig. 5.28). Associated obstructive and inflammatory changes of the submandibular gland should not be confused with invasion by tumor; salivary obstruction may also be a source of false-positive palpation of submandibular adenopathy.

Although uncommon, SCC of the RMT is an important subgroup of oral cavity tumors.[70,76,77] The RMT is at the junction of the oral cavity, oropharynx, and nasopharynx. As a result, tumors arising in the RMT can have complex patterns of spread with invasion of adjacent spaces[70,78–80](Fig. 5.18). In addition, RMT tumors have a propensity for early bone invasion with reported mandibular invasion in 12% to 53% of cases.[78–81]

Other less common subsites for SCC of the oral cavity include the buccal mucosa (Figs. 5.2, 5.4, and 5.14), gingiva, and hard palate. On imaging, it may be difficult or impossible to distinguish buccal from gingival tumors or gingival tumors arising on the lingual side of the mandible from those originating in the FOM. When evaluating buccal lesions or gingival lesions extending into the vestibule, obtaining an additional acquisition with “puffed cheeks” can be helpful for tumor visualization (Fig. 5.4). Because many of these tumors are close to the bone, there is a propensity for early bone invasion. In addition, cancers arising in the mucosa of the posterior hard palate may spread along the palatine branches of the maxillary nerve, through the palatine foramina to the PPF, with the potential for further retrograde PNS through foramen rotundum.

Determination of mandibular invasion is essential for proper staging of oral cavity tumors. Involvement of the mandible must be carefully evaluated, because it upstages the staging to T4. Sites of abutment of tumor against bone represent the most likely sites of bone invasion. With regard to surgical management, both the presence and extent of bone invasion, that is, superficial cortical invasion versus marrow invasion, are important and both CT and MRI may be warranted for optimal assessment.[70]

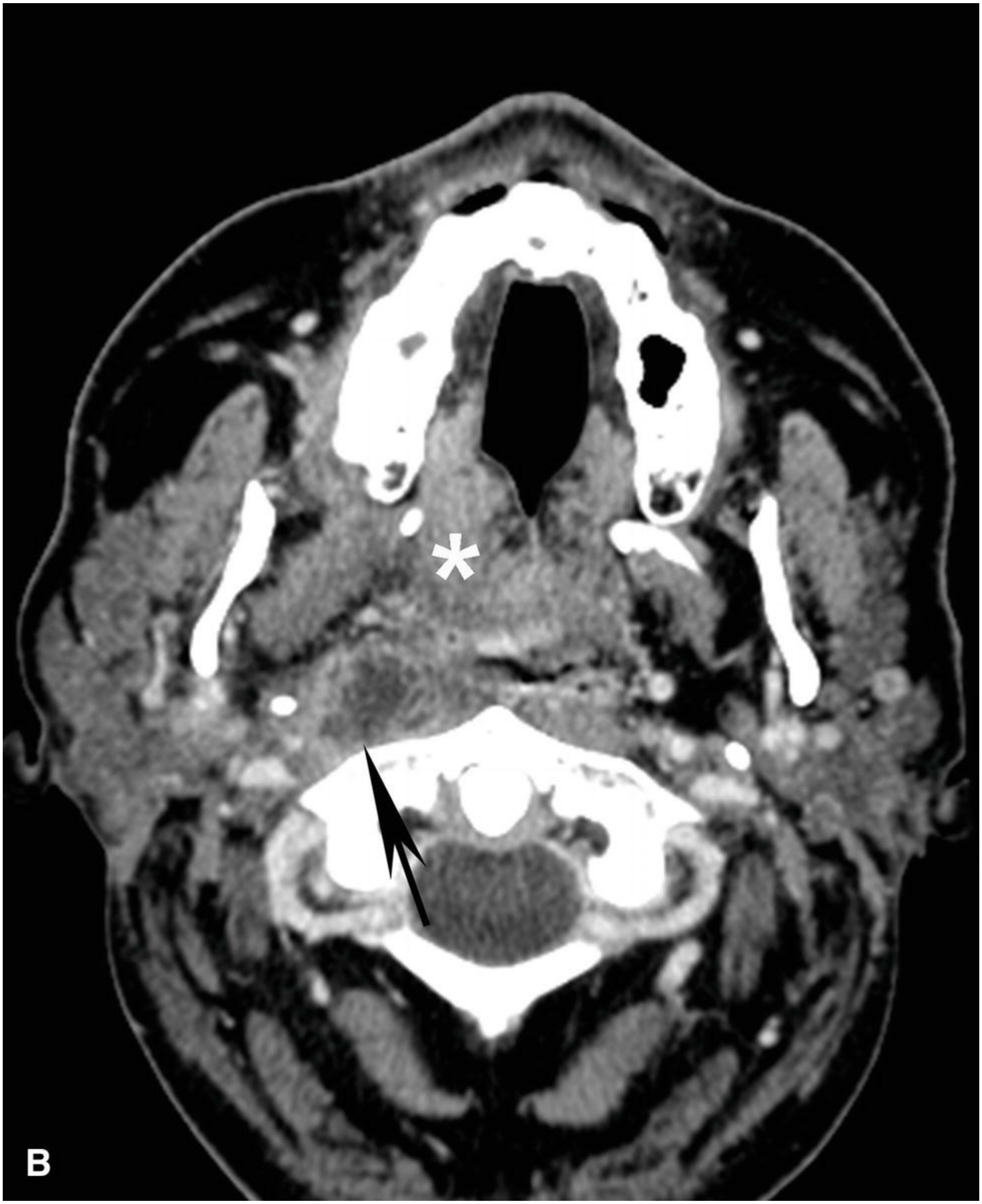
Oropharynx

The subsites in the oropharynx (OP) are the BOT, anterior and posterior tonsillar pillars and palatine tonsils, the soft palate, the glossotonsillar sulci, and the posterior and lateral oropharyngeal walls.[24,82] SCC accounts for 95% of neoplasms arising in the OP.[82]

SCC of the OP (SCCOP) has a dichotomous pathobiology that includes a classic subset that is associated with tobacco and alcohol use (Figs. 5.29 and 5.30) and a second subset that is associated with human papillomavirus (HPV) infection (Fig. 5.31). The HPV-positive SCCOP is responsible for the paradoxical increase in the age-adjusted incidence of OP carcinomas and represents a unique demographic, molecular, and clinical entity.[82–88] Typically, HPV-positive SCCOP patients present at a younger age, may lack or have limited exposure to classic environmental risk factors such as tobacco or alcohol use, and tend to have a more favorable prognosis.[88–93] Among HPV-positive SCCOPs, over 90% arise in the BOT or tonsils, or intervening glossopharyngeal sulcus (Fig. 5.31).

Figure 5.29. HPV-negative posterior oropharyngeal wall SCC. Axial contrast-enhanced CT from a 74-year-old male demonstrates an enhancing mass with submucosal extension to the lateral oropharyngeal wall on the right (*black arrowheads*). (V, Vallecula.)


PPS
T
A


B


C

Figure 5.30. Advanced HPV-negative oropharyngeal (OP) SCC. Axial contrast-enhanced CT images are shown from a 41-year-old man. **A:** There is very large OP mass (T) involving the tonsil but also the right soft palate (*large white arrowhead*). There is submucosal spread along the right

parapharyngeal space (PPS) with invasion of pterygoid muscles, indicating a T4 stage. The tumor abuts the right internal carotid (*small black arrow*) and invades the right parotid gland (*large white arrow*). More anteriorly, the lesion spreads to the base of the tongue (*double white arrowheads*). There is also extension into the region of right retromolar trigone (*small white single arrowhead*). **B:** At a level superior to **(A)**, there is asymmetric appearance of the right soft palate secondary to tumor spread (*white asterisk*). Note the irregular necrotic right retropharyngeal node (*black arrow*). **C:** Section obtained at a level below **(A)** demonstrates submucosal spread of tumor (*black asterisks*) with involvement of the base of tongue and glossotonsillar sulcus. There is a large necrotic right level II node abutting the tumor (*white arrowhead*). **D:** Axial section caudal to **(C)** demonstrates a component of the tumor invading the intrinsic and extrinsic muscles of the oral tongue (*white arrows*). There is also possible invasion of the right submandibular gland (SMG).


A

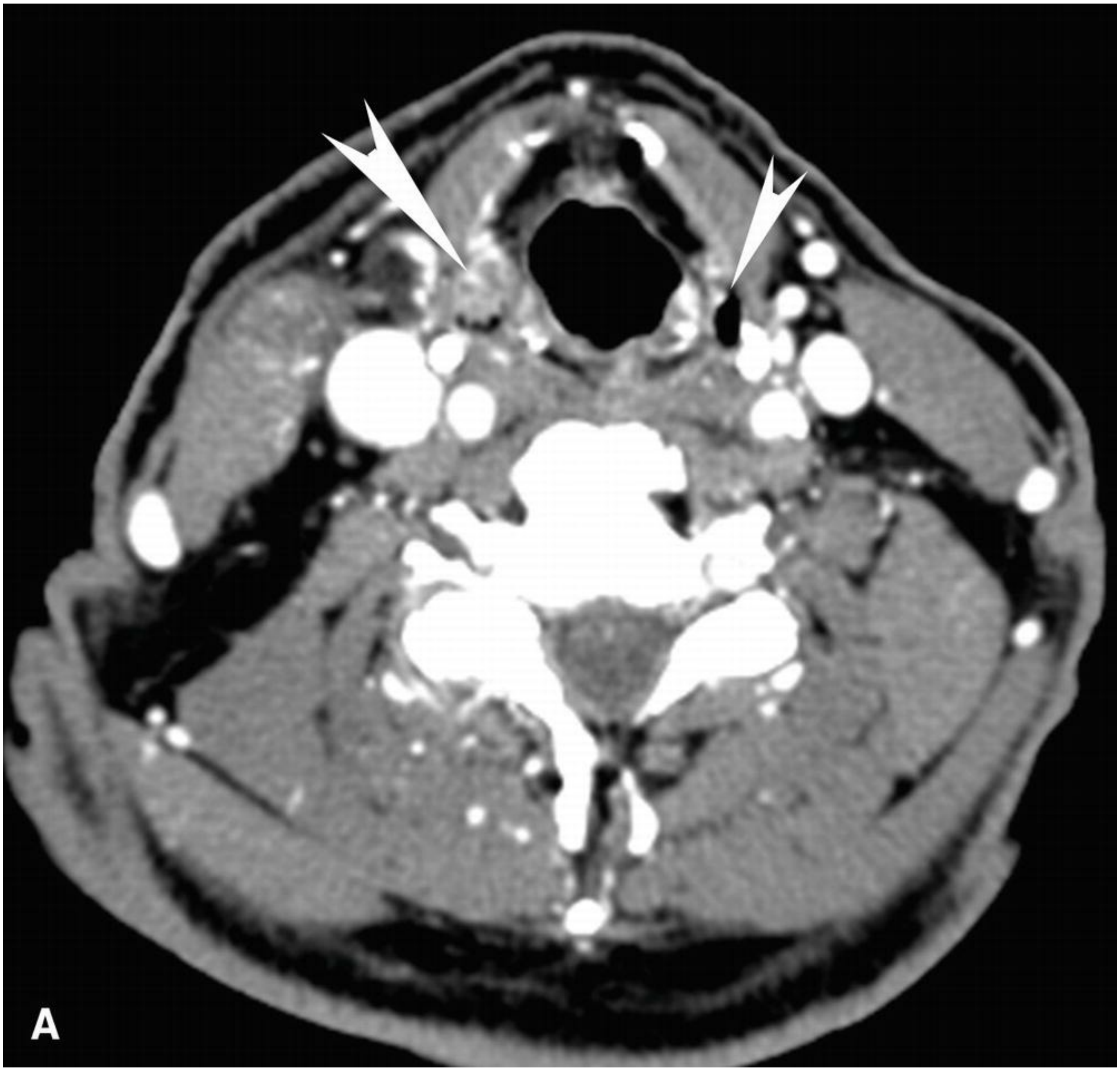
Figure 5.31. HPV-positive oropharyngeal (OP) SCC. Axial contrast-enhanced CT images are shown from a 59-year-old man. **A:** There is a mass in the right tonsil (*arrowheads*). The density of the mass is similar to the adjacent soft tissues, and it is difficult to appreciate its margins clearly, but the asymmetric enlargement is readily visible. **B:** Typical cystic level II node (*arrow*) associated with HPV-positive OP SCC.

Spread of tumor from the OP can occur to multiple adjacent spaces, either along adjacent mucosal surfaces or submucosally (Figs. 5.29 to 5.31). Tumors arising in the BOT may infiltrate the tongue musculature anteriorly (Fig. 5.30) or spread inferiorly into the epiglottis. Obliteration of the fat in the pre-epiglottis is a sensitive sign of tumor infiltration. Tonsillar region cancers can extend into the tongue anteriorly or superiorly into the nasopharynx (the latter upstages to T4). Because the size of the tonsils can vary, detection of tumor can sometimes be challenging. Any area of asymmetry needs to be carefully examined for changes in architecture or enhancement, and biopsy may be required in equivocal cases (Fig. 5.31). In general, tumor spread to the oral cavity, larynx (but not the lingual surface of the epiglottis), masticator space, nasopharynx, and skull base all upstage the disease and should be accurately determined. Encasement of the carotid artery is also important and must be carefully evaluated.

Consistent with their distinct pathobiology, HPV-positive and HPV-negative SCCOPs tend to have different imaging characteristics. There is a much higher incidence of cystic nodal metastases in HPV-positive compared to HPV-negative SCCOPs[88,94] (Fig. 5.31). HPV-positive SCCOPs are also less likely to invade adjacent muscle than HPV-negative tumors.[88] One study has also described a statistically insignificant trend for HPV-positive tumors having greater enhancement, appearing more exophytic, and having well-defined borders compared to HPV-negative tumors.[88]

Hypopharynx

The imaging approach to hypopharyngeal cancers is similar to the larynx, discussed in more detail in the next section. The first-line imaging modality for evaluation of hypopharyngeal cancers (Figs. 5.32 to 5.34) is CT in most centers.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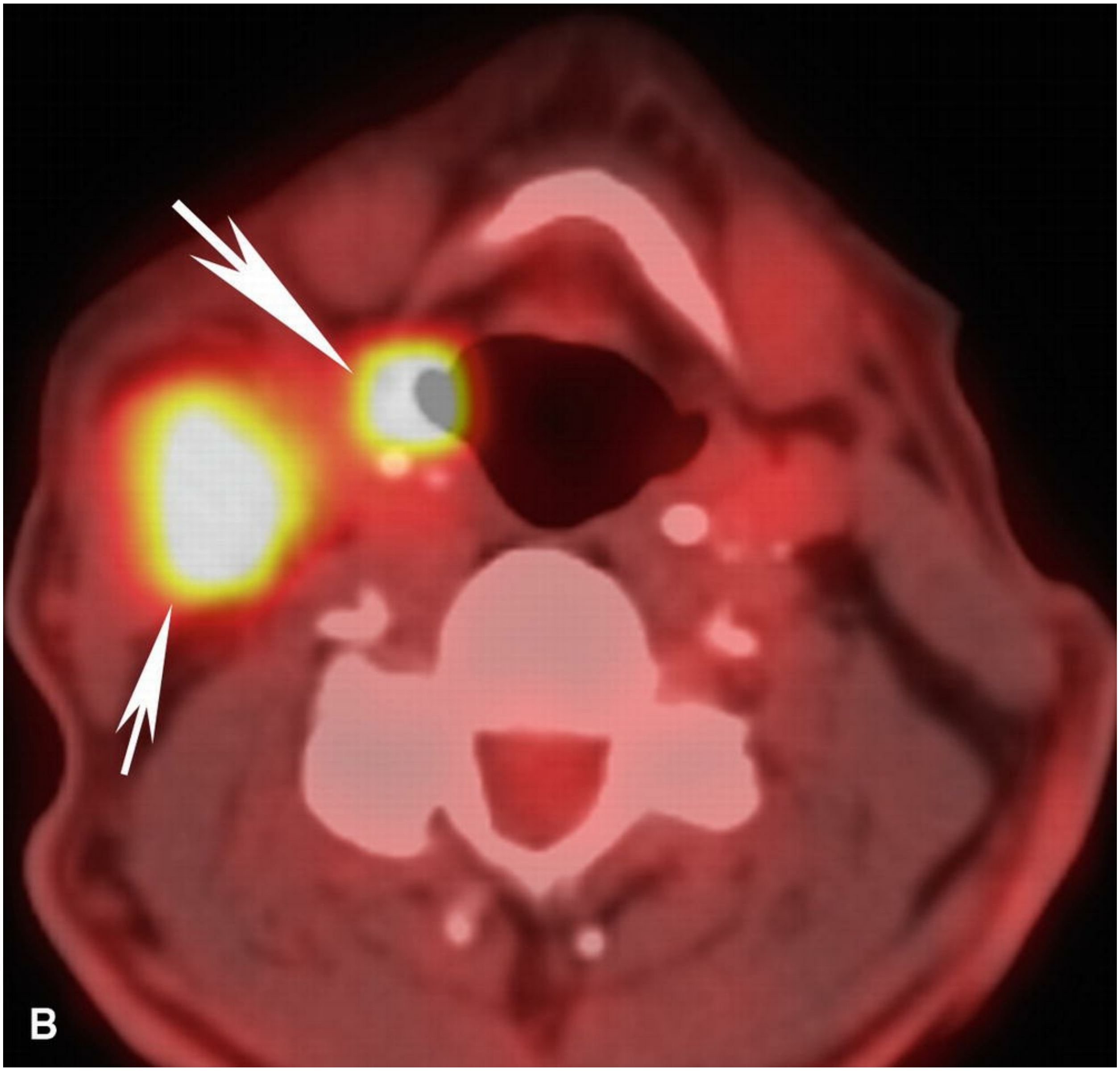


Figure 5.32. SCC of the hypopharynx. **A:** Axial contrast-enhanced CT from an 80-year-old man demonstrates a small right pyriform sinus SCC (*large arrowhead*). The lesion is subtle but visible on CT. Note the asymmetry when compared to the normal contralateral, aerated left pyriform sinus (*small arrowhead*). **B:** The lesion is well seen on PET (*large white arrow*). The PET scan (at slightly higher level) also demonstrates abnormal uptake within a large pathologic right level II to III nodal metastasis (*small arrow*).

Figure 5.33. SCC of the hypopharynx. Axial contrast-enhanced CT from a 77-year-old man demonstrates a heterogeneously enhancing hypopharyngeal mass (*black arrowheads*). The mass is centered in the hypopharynx, posterior to the arytenoid cartilages, distinguishing it from a primary arising in the larynx.


A

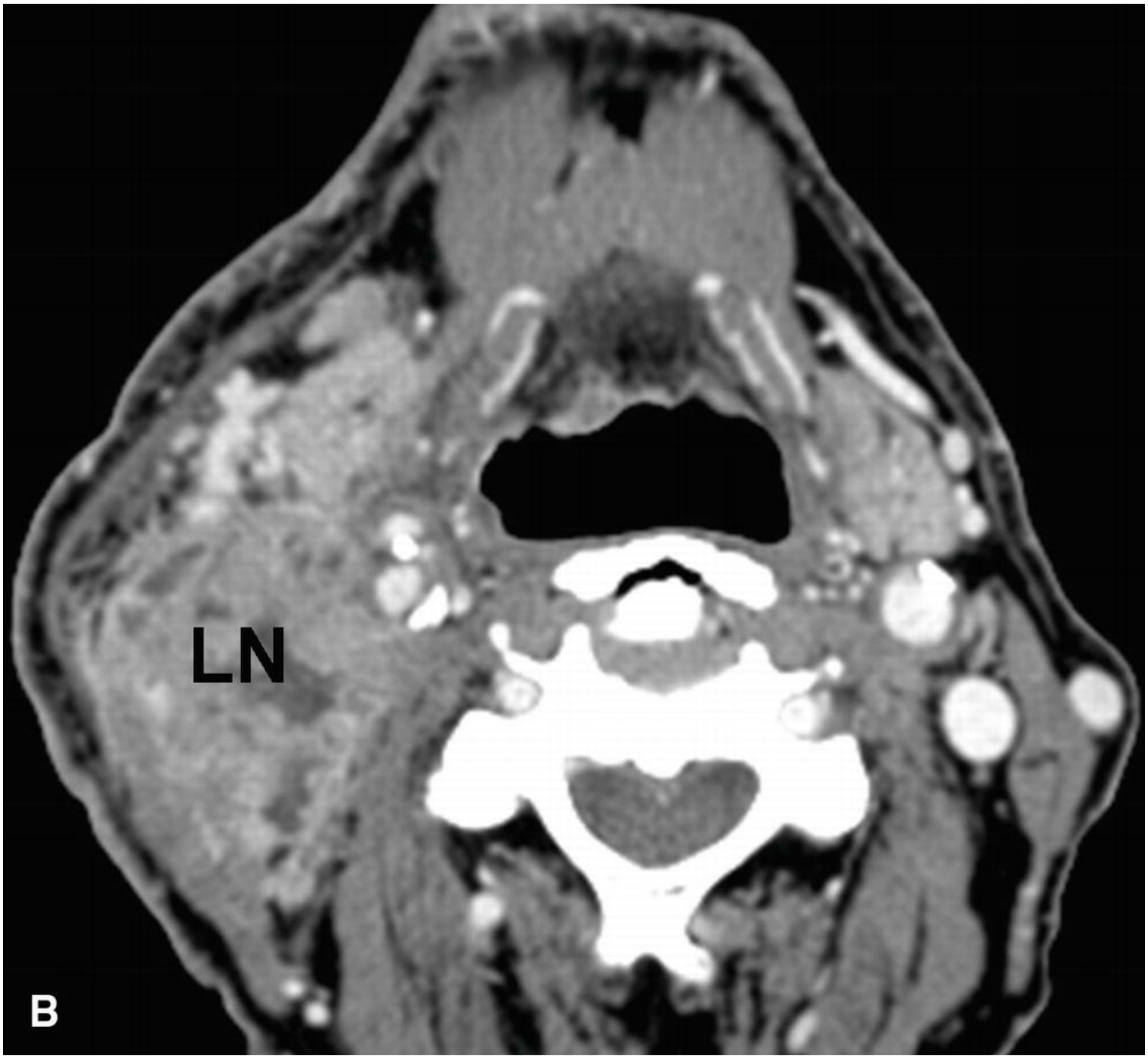


Figure 5.34. SCC of the hypopharynx. **A:** Axial contrast-enhanced CT image from an 88-year-old man demonstrates a lesion arising in the right pyriform sinus (*asterisk*), extending through the thyroarytenoid gap (*black arrowheads*), with invasion of the right paraglottic space (*arrow*) in the larynx. **B:** Image higher up in the neck demonstrates massive partly necrotic right level II lymphadenopathy (LN) with very irregular margins suggesting extracapsular spread of tumor.

Because of the intimate relation with the larynx, hypopharyngeal cancers can spread to the larynx (Fig. 5.34) and vice versa. Determination of their extent and involvement of specific laryngeal structures, including the thyroid cartilage, is essential for proper staging of these tumors. There are multiple

potential pathways of spread of hypopharyngeal carcinomas to adjacent structures. For tumors arising in the pyriform sinus, those arising on its medial wall may extend caudally to the arytenoid cartilage and cricoarytenoid joint.[95] Tumors arising on the lateral wall of the pyriform sinus may spread anteriorly to involve the laryngeal paraglottic fat and the posterior thyroid cartilage by spreading through the thyroarytenoid gap (Fig. 5.34). This is the area where the posterior paraglottic fat meets the pyriform sinus, extending between the two cartilages, and is readily seen on CT and MRI. This area should be carefully evaluated for spread of tumor and resultant obliteration of the normal fat in that area.

In addition to spread to the larynx, hypopharyngeal cancers can spread superiorly, inferiorly, or posteriorly, and this needs to be carefully evaluated and documented. Lateral extension of these tumors could result in the tumors coming in contact with the carotid artery. Invasion of cricoid or thyroid cartilage, even when focal or partial, upstages a tumor to a T4a stage.[95,96] Furthermore, because of the rich lymphatic drainage of the hypopharynx, tumors arising in this area commonly present with nodal metastases. For SCCs of the hypopharynx, the main node groups involved by nodal spread are level II, III, IV, and VB nodes.

Larynx

CT is the first-line modality for evaluation of laryngeal tumors. MRI can also be used to evaluate the larynx, but obtaining high-quality images may be challenging because of inability of patients to remain motionless for prolonged periods of time. Therefore, MRI is usually performed as a complementary exam to the CT scan, for example, for evaluation of cartilage invasion as discussed below. Ideally, this should be performed with a surface coil as a targeted high-resolution acquisition.

When evaluating the location of a laryngeal tumor on axial images, the supraglottic location of a tumor can be reliably determined by identification of fat in the paraglottic space (Fig. 5.35). This is the space between the laryngeal mucosa and the inner lamina of the thyroid cartilage, and in the supraglottic region, the paraglottic space is made up of fat at the level of the false cords (Fig. 5.35). On the other hand, at the level of the true vocal cords, the thyroarytenoid muscle occupies most of the paraglottic region, and there should not be paraglottic fat visible. This serves as a landmark for the level of

true vocal cords on axial images, as does the vocal process of the arytenoid cartilage (Fig. 5.36).


*
B

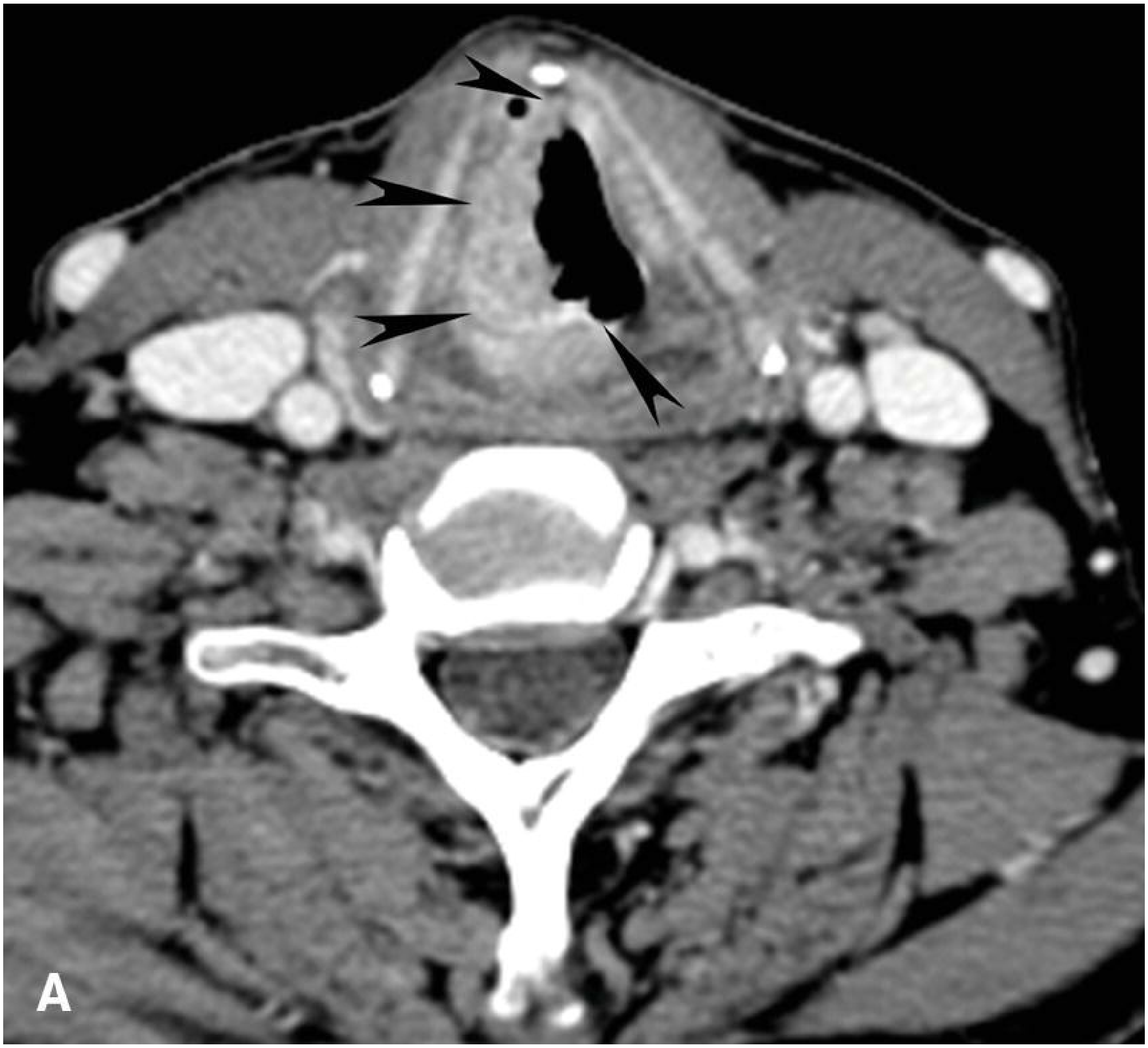
Figure 5.35. SCC of the larynx. Axial CT images are shown from an 81-year-old woman with a transglottic SCC at the anterior commissure. **A:** Image obtained at the level of the false cords demonstrates a small fluid-filled, obstructive internal laryngocele (*black arrowhead*). When encountered, this finding always mandates careful scrutiny in order to identify a potential obstructive cancer. Note the presence of paraglottic fat at this level (e.g., contralateral normal paraglottic fat marked by *white arrowhead*). This is a reliable indicator of supraglottic location on axial images. **B, C:** Images obtained more caudally demonstrate a tumor involving the midline anterior commissure and extending bilaterally (*asterisk*). Note

variable ossification of the thyroid cartilage with component of nonossified thyroid cartilage (*small black arrowheads*).

Figure 5.36. SCC of the larynx. Axial CT image from a 57-year-old woman

with a glottic and subglottic laryngeal cancer. There is tumor (*asterisk*) involving the left true cord with associated asymmetry of that cord. Note the absence of significant paraglottic fat on the normal contralateral side (*black arrow*), a landmark for the level of true cords on axial images.

As in other parts of head and neck, identification of asymmetry and infiltration of fat is important for determination of tumor invasion. In the supraglottic larynx, one should assess for obliteration of paraglottic fat. If a section can be found below the site of tumor invasion where the paraglottic fat is not obliterated, then the lesion can be confidently considered as a supraglottic tumor. However, if a tumor extends to the true cord, evaluation is more challenging. For these lesions, involvement is suggested by comparing the width of suspected cord to the contralateral side and evaluating for asymmetry (Figs. 5.36 and 5.37), although this evaluation is less reliable, particularly for small tumors. Evaluation of subglottic extension of tumor can also be challenging. In this area, the only sign of tumor may be subtle irregularity and enhancement of the mucosal surface of the lumen with mild associated luminal distortion (Figs. 5.37). Evaluation in other planes such as the coronal or sagittal plane can also be helpful for assessment of these lesions. Similar to other sites in the head and neck, superficial mucosal lesions are best assessed clinically.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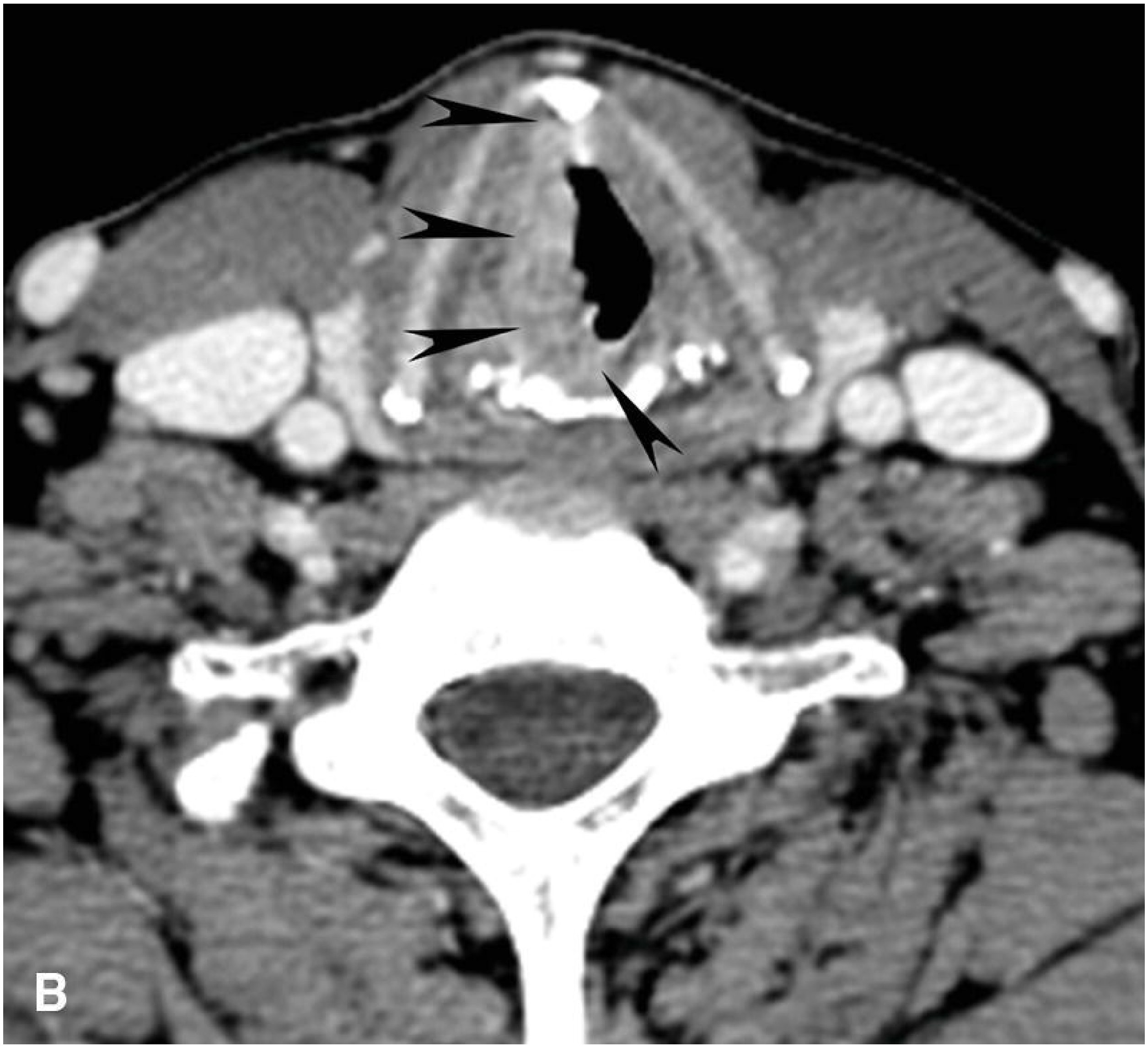
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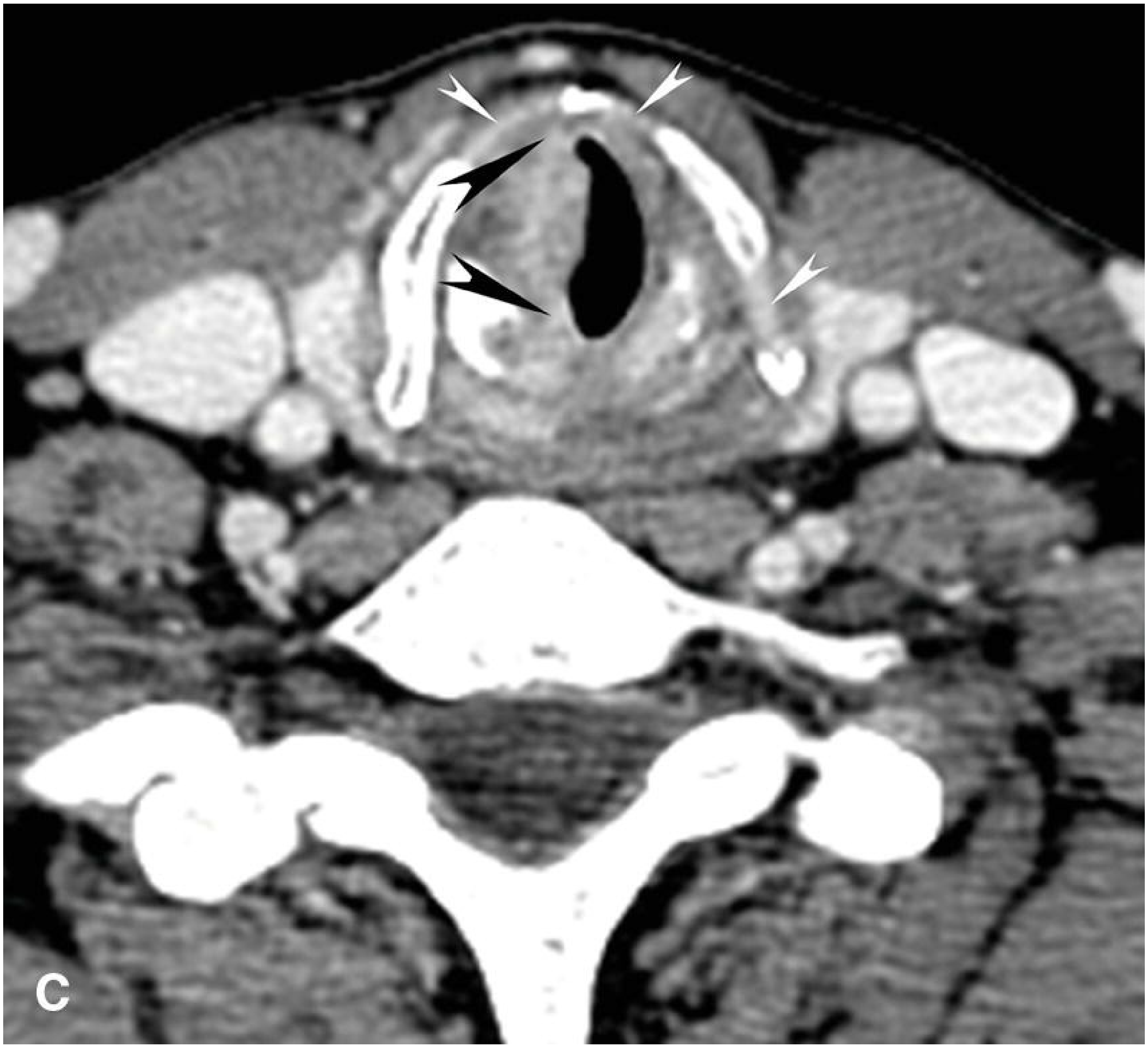


Figure 5.37. SCC of the larynx. Axial CT images (**A**, upper glottic level; **B**, lower glottic level; **C**, immediate subglottic level) from a 48-year-old male smoker demonstrate a right transglottic laryngeal cancer (*black arrowheads*). The lesion extends to the anterior commissure and also crosses the midline posteriorly. Note incomplete ossification of the thyroid cartilage with interspersed areas of ossification and nonossification, especially in **(C)** (*small white arrowheads*).

Determination of the presence or absence of laryngeal cartilage invasion is an important part of staging of laryngeal and hypopharyngeal tumors. For laryngeal cancer, tumors involving only the inner cortex of the thyroid cartilage are classified as T3 stage, but those with through and through

invasion, that is, involvement of both the inner and outer cortex, are staged as a T4 lesion.[96,97] This is unlike hypopharyngeal tumors, where even localized cartilage invasion leads to a T4a designation. It should be noted that extralaryngeal spread, with or without cartilage invasion, will also lead to a T4a designation.[96]

CT can generally identify gross cartilage invasion reliably, but determination of early and partial cartilage invasion can be challenging.[98,99] One of the challenges in evaluation of cartilage invasion is the variable appearance and ossification of thyroid cartilage.[96,100–102] The main criteria used for evaluation of thyroid cartilage invasion are sclerosis, erosion (minor areas of osteolysis), lysis (major areas of osteolysis), and extralaryngeal spread of tumor.[99] Sclerosis is a sensitive sign but is very nonspecific and unreliable because it can be seen in normal cartilage in older patients. Erosion, lysis, and extralaryngeal spread are less sensitive but much more specific and reliable signs of cartilage invasion. One must be cautious in stating that there is involvement of cartilage on the basis of a defect in the calcification of a cartilage alone because the variability in calcification makes this finding unreliable (Figs. 5.37). The most definite sign is demonstration of tumor beyond the external surface of the cartilage. MRI can also be used to evaluate cartilage invasion but with variable success and may overestimate cartilage invasion because of reactive changes and edema that may lead to a false-positive diagnosis of cartilage invasion.[96,101,103–105] Similar to evaluation of bone invasion, it is important to compare the signal changes in the cartilage to adjacent tumor. If similar, tumor invasion should be suspected.

POSTTREATMENT IMAGING IN HEAD AND NECK CANCER

Overview

The modern management of head and neck cancer involves multidisciplinary efforts, often including oncologic surgery, plastic and reconstructive surgery, radiation therapy, and chemotherapy. Complicated and variable approaches to surgical resection, local tissue reconstruction, neck dissection, radiation

therapy, and concurrent versus neoadjuvant chemotherapy regimens can complicate imaging findings during and after treatment.[106] The goal of imaging in the posttreatment stage is in large part to identify evidence of viable residual disease and/or recurrence. However, differentiating posttreatment changes from residual or recurrent tumor can be challenging due to altered anatomy, radiation changes, and postsurgical scarring. Furthermore, radiation therapy may induce tissue changes including edema, inflammation, and fibrosis that can make assessment challenging.

The main imaging modality used in the evaluation of the posttreatment neck is CT, with MRI, PET/CT, and US offering additional, complementary information. US and CT are readily available, enable rapid image acquisition, and are helpful in the acute setting for clinical diagnosis. MRI provides superior soft tissue contrast. Diffusion-weighted MR imaging can be a useful tool to differentiate tumor recurrence from normal posttreatment changes but can be technically challenging to optimize and can be limited in its spatial resolution. Combined imaging with PET and CT (PET/CT) offers a highly sensitive technique for detection recurrence of head and neck cancer in the posttreatment setting. PET/CT performed <10 to 12 weeks after completion of radiation therapy has a high false-positive rate because of the presence of postirradiation inflammation, edema, or distortion. However, PET/CT performed after 12 weeks has a very high negative predictive value.[107,108] In this section, we will review key posttreatment imaging appearances including tumor recurrence, postsurgical complications, mucosal necrosis, osseous complications, radiation-induced brain necrosis, and radiation-induced neoplasm.

Treatment Methods and Expected Posttreatment Imaging Findings

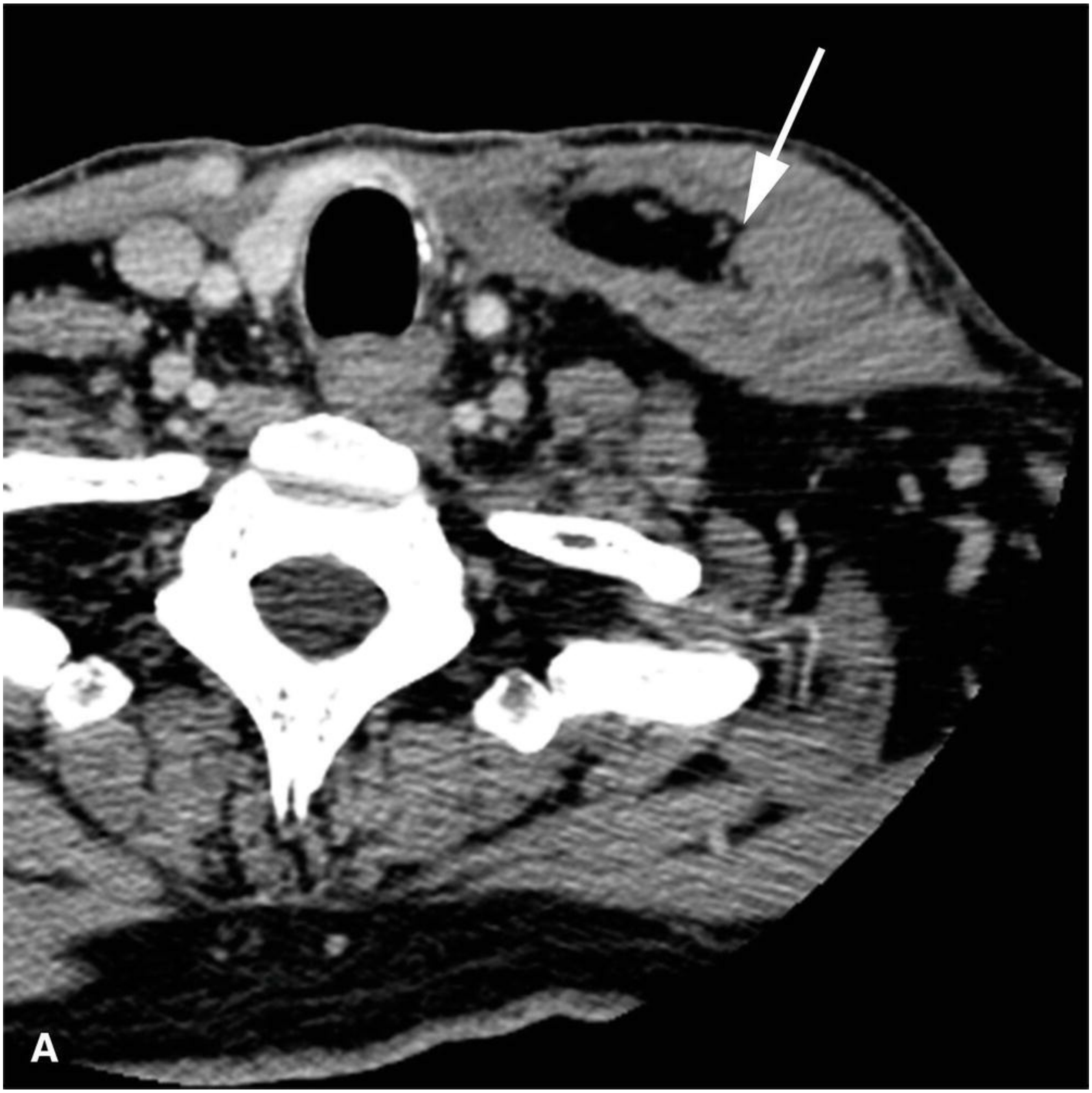
The management of early-stage head and neck cancer typically consists of single-modality treatment with either radiation therapy or surgery. Multimodality treatment consisting of a combination of curative surgery followed by adjuvant radiation therapy, with or without chemotherapy, is typically employed for locally advanced head and neck cancer (stage III or IV) without distant metastases. Oral cavity and sinonasal carcinomas are typically treated with surgery followed by adjuvant radiation therapy, with or without chemotherapy, depending on the histopathologic findings and nodal

stage. Primary treatment with chemoradiation is used for locally advanced head and neck cancer, particularly for nasopharyngeal, oropharyngeal, hypopharyngeal, and laryngeal carcinomas.

Surgery With or Without Reconstruction

Curative resection requires a wide local excision with negative margins. The physiologic and anatomic complexity of the neck requires complex reconstructive techniques to close the defect and maximize posttreatment function. With regard to imaging, it is critical to compare the postoperative study with a recent, same-modality preoperative scan. Depiction of the postoperative appearance of the countless possibilities of postresection head and neck surgery is beyond the scope of this chapter, but some examples are presented below.

There are two main types of flap reconstruction, free and pedicled, for repair of a surgical defect. Free flap reconstructive technique (free tissue transfer) involves the transfer of distant tissue that is vascularized by local vessels, with anastomosis to the tissue defect by using microvascular techniques (Fig. 5.38). Pedicled or rotational flap reconstruction involves elevation and rotation of nearby donor tissue, usually muscle or mucosa, to cover a defect, with preservation of the original arterial and venous structures.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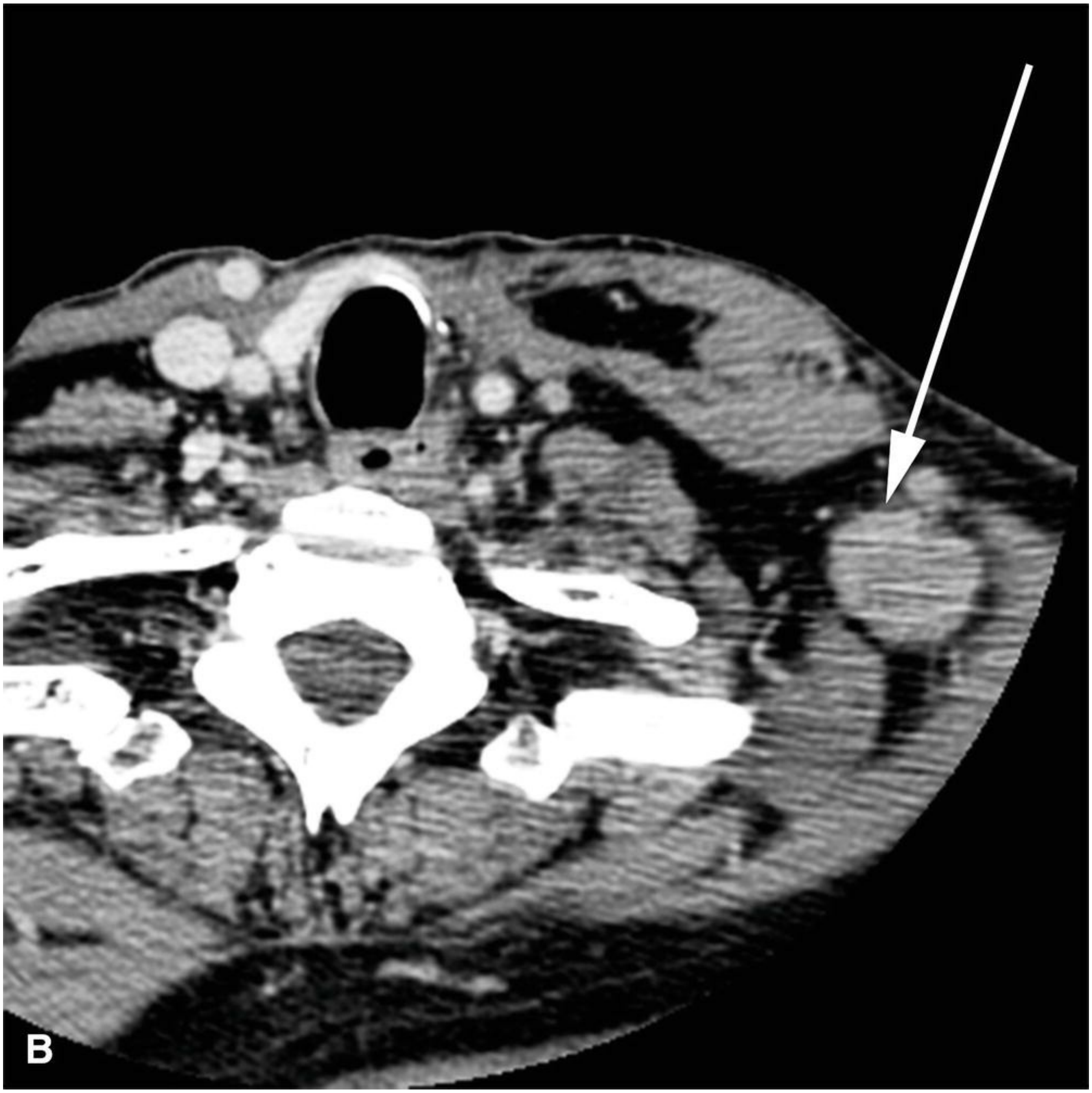

Figure 5.38. A 57-year-old man with recurrent squamous cell carcinoma to the left neck was treated with a left neck dissection, brachytherapy, and flap reconstruction. Five months after the surgery, a second recurrence was identified adjacent to the operative bed. **A:** Postoperative baseline CT of the neck with contrast shows expected findings of a pedicled flap (*arrow*). **B:** Subsequent, a CT of the neck with contrast reveals a recurrent mass is evident posterolateral to the flap (*arrow*).

Myocutaneous flaps are initially depicted as a mass with soft tissue attenuation and variably enhancing soft tissue intensity on MRI, representing

muscle. Fatty flap components suppress or become dark with fat suppression techniques and do not enhance. These flaps will gradually show denervation atrophy, which causes volume loss and fatty replacement of the muscle. Sharp boundaries exist between the flap and the adjacent normal structures, which is an important sign indicating benignity. It is therefore important to assess the superior and inferior margins of the flap, where local recurrence most commonly occurs. The muscular components of myocutaneous flaps show a wide spectrum of enhancement on MRI after contrast material administration, ranging from almost no contrast enhancement to diffuse intense enhancement. These enhancement characteristics do not predict failure of the flap and should not be misconstrued as tumor recurrence. The presence of striations in the muscular component of a graft is expected and generally indicates a healthy flap, helping to avoid misdiagnosis if the muscle enhances.[109] Normal flaps do not enhance on CT.

Neck Dissection

Radical neck dissection, modified radical neck dissection, and selective neck dissection are the three major types of neck dissection. Radical neck dissection involves the removal en bloc of all of the ipsilateral lymph nodes (levels I to V), the sternocleidomastoid muscle, internal jugular vein, submandibular gland, and spinal accessory nerve. Extended radical neck dissection is the same as radical neck dissection but includes the removal of additional nodes (levels VI and VII) and/or nonlymphatic structures such as the internal carotid artery, hypoglossal nerve, and vagus nerve. Indications for radical neck dissection are extensive cervical involvement or lymph nodes with gross extracapsular spread and invasion into the adjacent tissues.

Modified radical neck dissection is the same as radical neck dissection but preserves the sternocleidomastoid muscle, internal jugular vein, submandibular gland, and/or spinal accessory nerve. Modified radical neck dissection is indicated in patients with less spread and invasion. Modified radical neck dissection has some advantages; for example, preservation of the spinal accessory nerve prevents the development of adhesive capsulitis (frozen shoulder) and modified radical neck dissection causes less cosmetic deformity than radical neck dissection.

There are four subtypes of selective neck dissection. These are the supraomohyoid type (levels I to III), the lateral type (levels II to IV), the

posterolateral type (levels II to V), and the anterior compartment type (levels VI and VII). Selective neck dissection preserves the functional and cosmetically relevant structures (see Fig. 5.38 for depiction of a posterolateral type; other types are shown in figures below).

Radical and modified radical neck dissections typically have obvious and expected imaging findings of absence of the resected tissue and lymph nodes. Selective neck dissections may have more subtle findings, especially when limited to one or two stations. There is typically formation of fibrosis or scar surrounding the carotid sheath, which is evident as increased density on CT and low to intermediate signal intensity on T1- and T2-weighted MR images. Neck dissection obliterates normal fat planes, which makes identifying nodal recurrence more challenging.

Radiation Therapy

External beam radiation therapy (EBRT) is the main type of radiation therapy used for the treatment of cancer of the head and neck. EBRT includes three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, and stereotactic radiosurgery. EBRT uses photon, electron beam, or proton beam radiation delivered from a source external to the patient. Definitive doses of radiation with EBRT for head and neck cancer consist of 66 to 70 Gy delivered daily during a period of ~7 weeks. Intensity-modulated radiation therapy has become the preferred technique for administering photon external beam radiation as it allows sparing of at-risk organs, including the parotid glands, pharyngeal constrictor muscles, and orbits.

Radiation therapy reactions are divided into early and late changes based on 90 days from treatment. Early reactions are reversible in most cases. Late complications may take months to years to emerge and are often irreversible. The early complications of radiation therapy are seen frequently, particularly oral mucositis and skin desquamation, and completely resolve within a few weeks after completion of radiation therapy. Late complications include xerostomia, dysphagia, accelerated dental caries, soft tissue necrosis, osteoradionecrosis, radiation-induced vascular complications, and radiation-induced neoplasms. The severity and duration of radiation reactions may be exacerbated by multiple factors including the smoking and alcohol consumption habits.

Imaging findings of early radiation reactions are thickening of the skin and platysma, stranding of the subcutaneous fat, edema and fluid in the retropharyngeal space, increased enhancement of the major salivary glands, thickening and increased enhancement of the pharyngeal walls, and thickening of the laryngeal structures (Fig. 5.39). Late reactions to radiation therapy include atrophy of the salivary glands and thickening of the pharyngeal constrictor muscle, platysma, and skin.

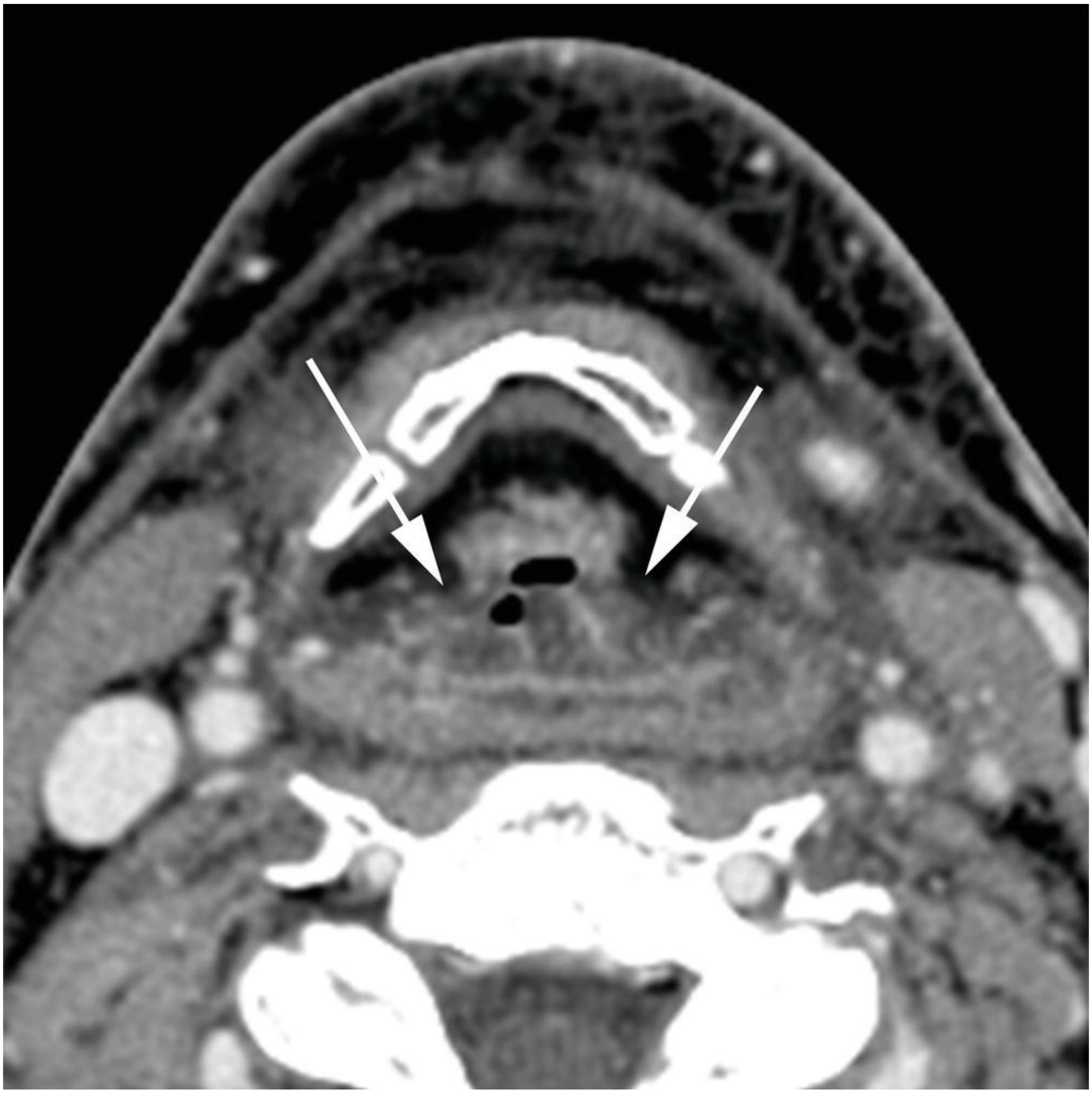

Figure 5.39. A 60-year-old male with T2 N2C squamous cell carcinoma of the left base of the tongue who was treated with chemoradiation including a

radiation boost. CT of the neck with contrast reveals significant supraglottic edema (*arrows*) and near complete airway obliteration.

Posttreatment Imaging Appearance of Tumor Recurrence and Various Complications

Tumor Recurrence

Tumor recurrence deep to flap reconstructions is often not evident visually or palpable. The most common locations for tumor recurrence are in the operative bed and at the margins of the surgical site (Fig. 5.40). Tumors are most likely to recur within the first 2 years after treatment and may recur within weeks after surgery. On imaging, tumor recurrence can manifest as a slightly expansile lesion in the operative bed or as progressive thickening of soft tissues deep to the flap (Fig. 5.38). CT typically demonstrates recurrence as an infiltrating slightly hyperattenuating mass with enhancement, with or without bone destruction. Tumor recurrence typically enhances greater than skeletal muscle (Fig. 5.41). Therefore, if a suspected mass has lower attenuation than that of muscle on CT, it is unlikely to be a malignancy and often is related to edema. MR imaging demonstrates tumor recurrence as an infiltrative mass with intermediate T1-weighted signal intensity, intermediate to high T2-weighted signal intensity, and enhancement.


A

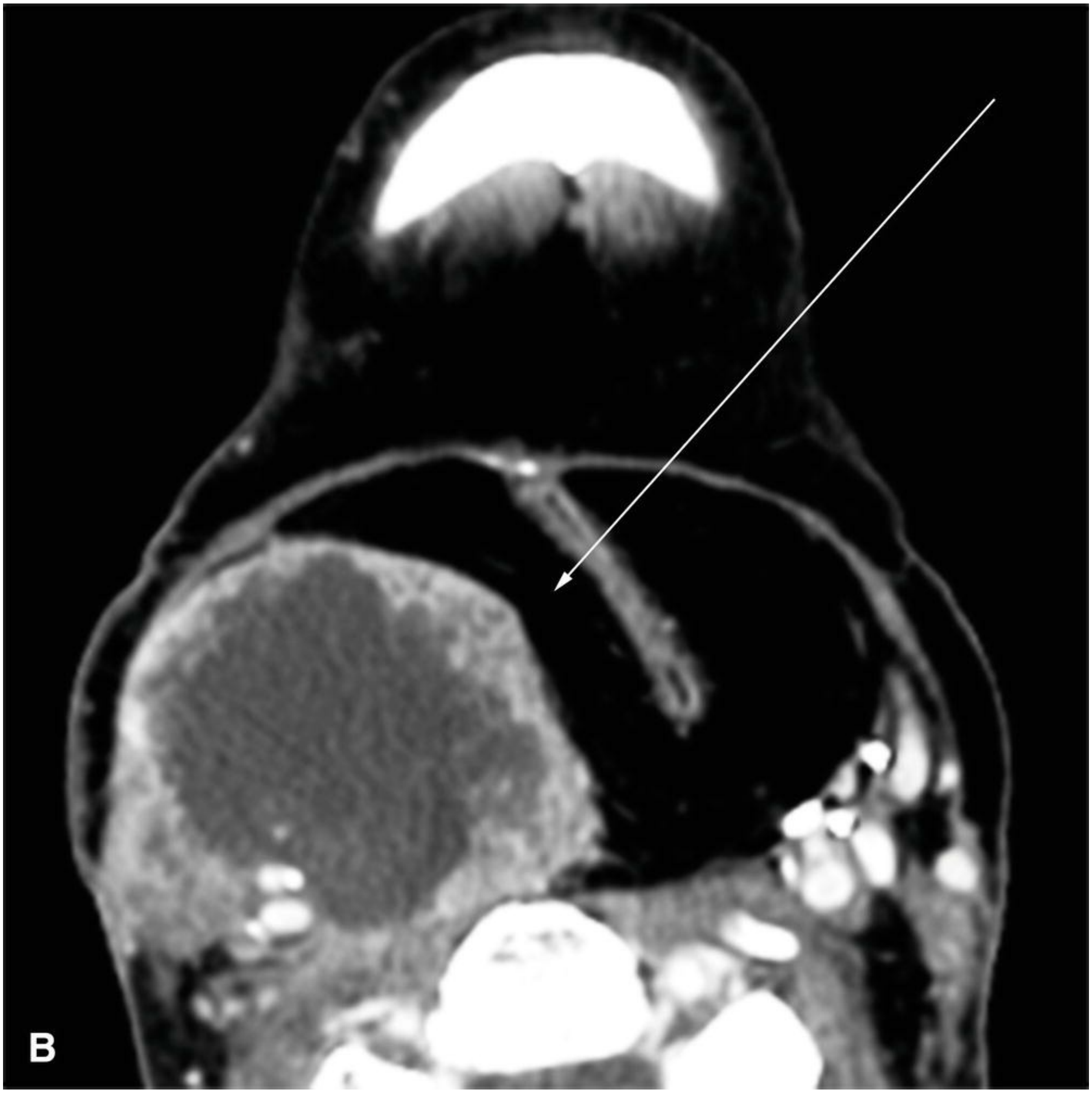

Figure 5.40. A 56-year-old woman who required total laryngopharyngectomy and free flap reconstruction for recurrent laryngeal carcinoma. This sequence demonstrates evolution of massive recurrence. **A:** CT of the neck with contrast displayed a small enhancing nodule that developed along the right carotid artery (*arrow*). **B:** A subsequent CT of the neck with contrast clearly revealed to be a site of dramatic recurrent cancer (*arrow*).


A

Figure 5.41. A 50-year-old man with T1 N2B squamous cell carcinoma of the right tonsil treated with induction chemotherapy and concurrent chemoradiation. Axial postcontrast CT imaging obtained 2 **(A)** and 12 **(B)** months following completion of therapy reveals the development of an area of mucosal ulceration (*short arr*ow in **B**), which had previously been normal (*arrow* in **A**). Thick marginal enhancement surrounding the mucosal defect (*long arrow* in **B**) was regarded as concerning and proved to be tumor recurrence.

Cervical lymph node metastases occur in well-defined patterns, and an

understanding and familiarity with these patterns is helpful for making an early diagnosis. Oral cavity carcinomas frequently metastasize to level I, II, and III nodes. Oropharynx and supraglottic laryngeal cancers metastasize to level II, III, and IV nodes. Nasopharynx, hypopharynx, and BOT carcinomas frequently metastasize to level II, III, IV, and V nodes. Thyroid cancer typically spreads to level III, IV, and VI nodes. Bilateral lymph node metastases are more frequently seen with nasopharyngeal, oropharyngeal, BOT, and supraglottic laryngeal carcinomas.

The detection of lymph node recurrence and metastases is more difficult following neck dissection and radiation therapy because of the obliteration of fat planes. Lymph node recurrence and metastases can be identified based on relative hyperenhancement and expansive features (Fig. 5.42). Similar to its use for the primary tumor site, diffusion-weighted MR imaging can be useful in the characterization of enlarged posttreatment lymph nodes that manifest as low signal intensity on apparent diffusion coefficient (ADC) maps.[110]

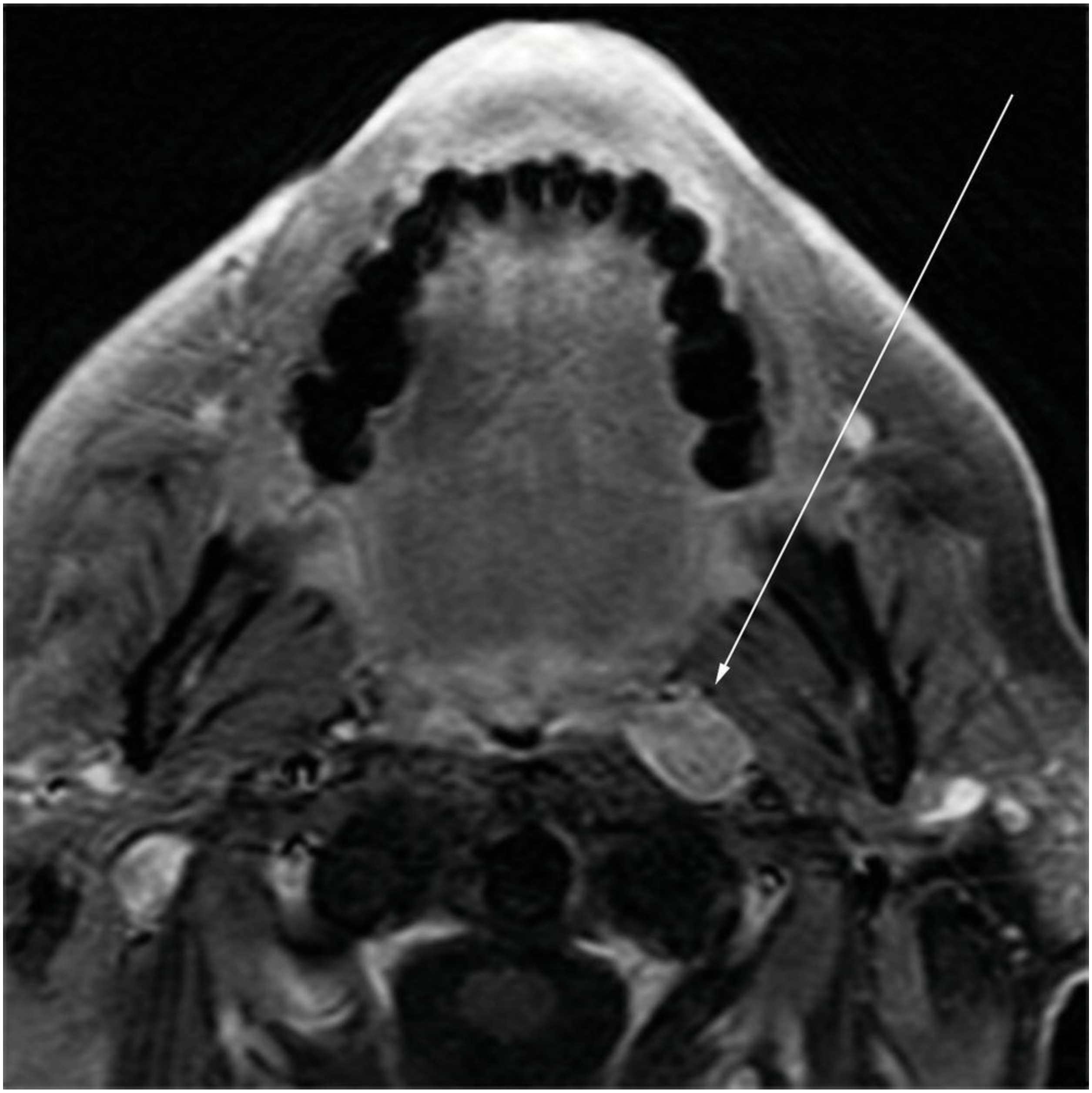

Figure 5.42. A 55-year-old man status postsurgery and radiation for olfactory neuroblastoma. Axial T1-weighted postcontrast image reveals an enhancing retropharyngeal nodal metastasis (*arrow*) 3 years after therapy.

Perineural tumor spread is a unique form of tumor recurrence, and has the same appearance as when it occurs prior to therapy. Perineural tumor spread in the head and neck is most commonly seen with cutaneous and mucosal SCC, followed by adenoid cystic carcinoma and other less common malignancies. The imaging findings of perineural tumor spread are nerve enlargement with enhancement, foraminal enlargement, obliteration of fat

planes, and replacement of the skull base foramina with soft tissue (Fig. 5.43). Perineural tumor spread is more readily identifiable at MR imaging, given the greater soft tissue contrast, but can be seen at CT. Close correlation with prior images and clinical symptoms can help distinguish perineural tumor spread from treatment-related changes. Follow-up imaging may be required in equivocal cases.[26,111]


B


C

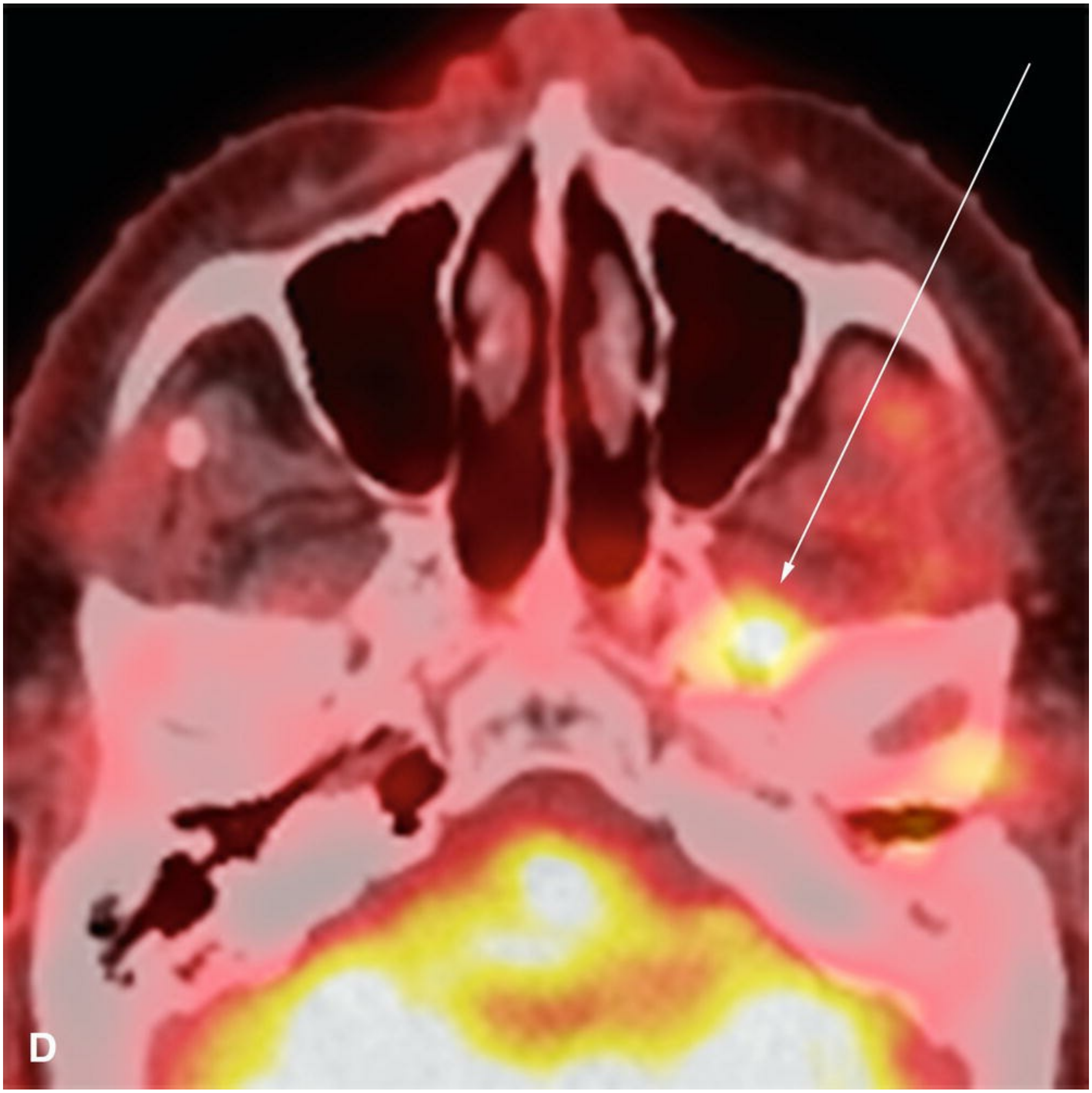

Figure 5.43. A 58-year-old man with previously treated left preauricular squamous cell carcinoma recurrent along the auriculotemporal branch of the mandibular nerve. Contrast-enhanced axial CT images, soft tissue windows **(A, B)**, bone algorithm **(C)**, reveal abnormal enhancement (*arrows*) within **(B)** and most notably beneath **(A)** the left foramen ovale and subtle foraminal enlargement (*arrow* in **C**) indicating perineural tumor spread. FDG-PET/CT **(D)** shows hypermetabolism associated with these changes of perineural disease recurrence (*arrow*).

Complications after Surgery

Surgical complications tend to occur early and include wound infection, abscess, fistula, flap necrosis, hematoma, chylous fistula, and serous retention (Fig. 5.44). Multiple risk factors have been reported, including preoperative radiation therapy, preoperative chemoradiation therapy, prior tracheotomy, long duration of surgery, type of flap, age, primary tumor stage, medical complications, malnutrition, anemia, tobacco use, and a history of habitual alcohol consumption.


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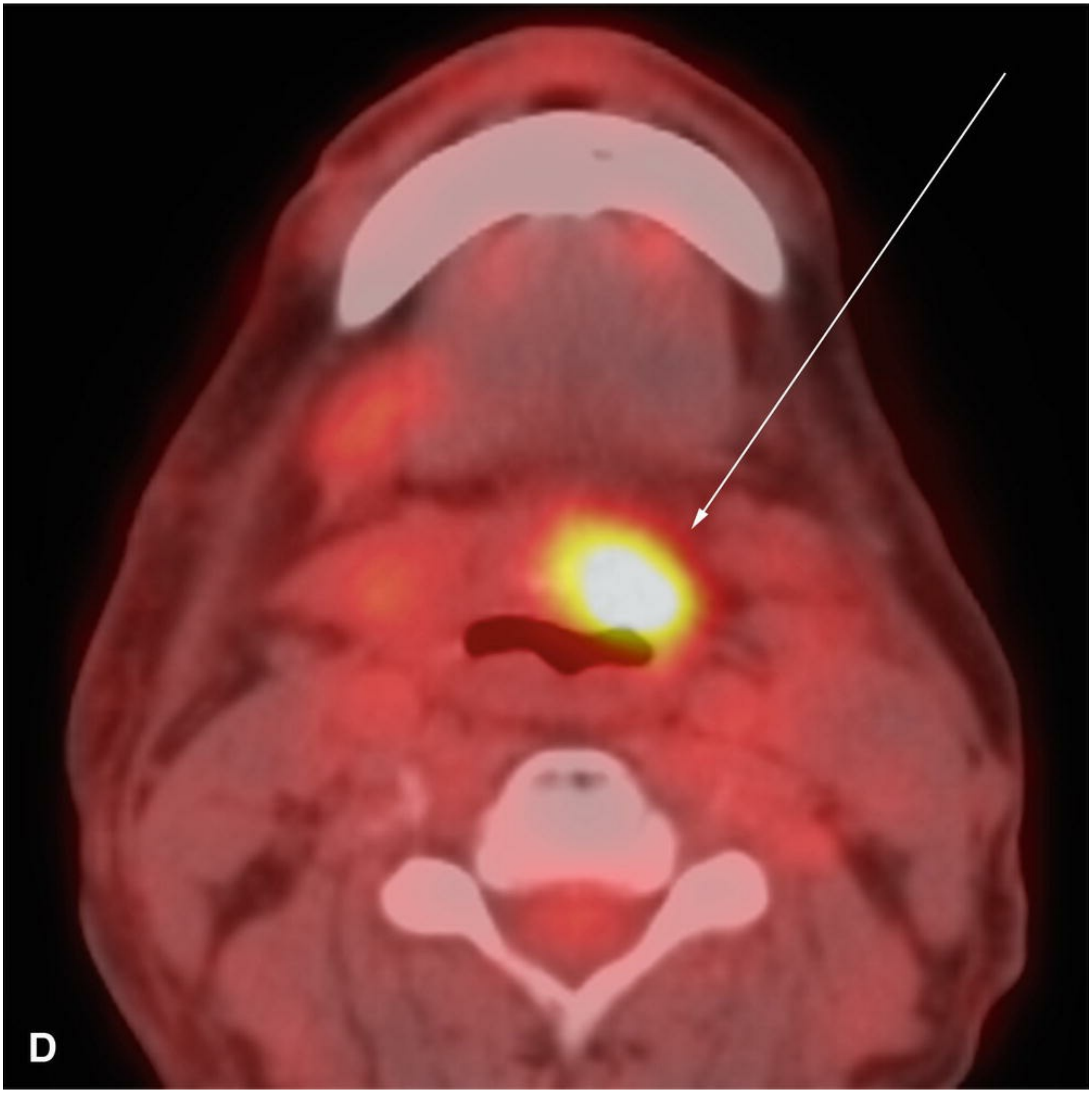


Figure 5.44. A 58-year-old man treated with induction chemotherapy, total laryngectomy, bilateral neck dissection, and postoperative radiation therapy for a T4a N2C M0 squamous cell carcinoma of the larynx. A posttreatment CT of the neck with contrast in axial **(A)** and sagittal **(B)** reveals a mucosal dehiscence (*asterisk*) along the neopharynx. There was also abnormal enhancement **(C)** and hypermetabolism on FDG-PET/CT **(D)** along the base of the tongue (*arrow*). Biopsy of this site confirmed recurrent squamous cell carcinoma.

After surgery, a fluid collection is sometimes seen, and serous retention

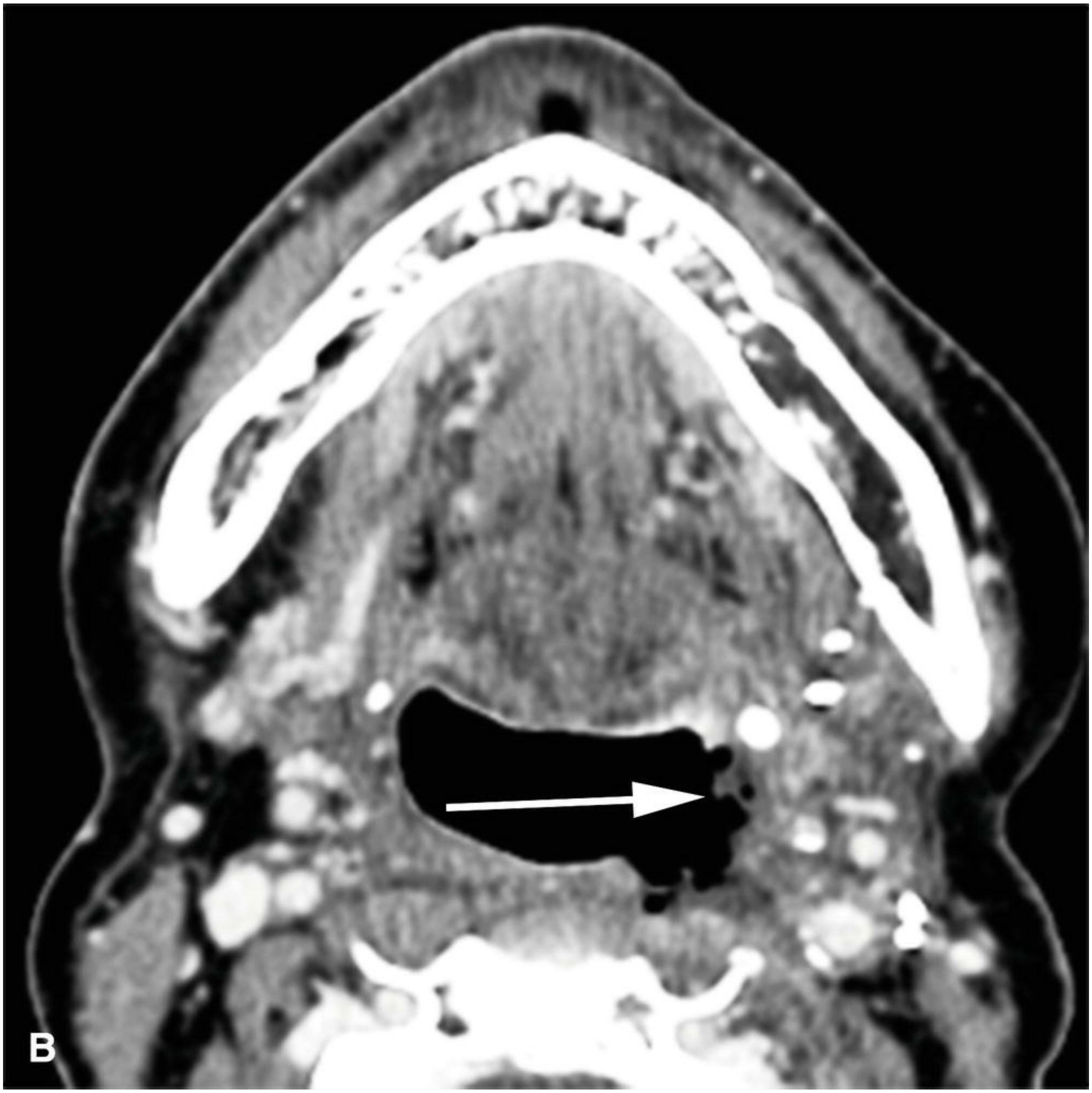
may often resolve spontaneously, requiring no further treatment. Chylous fistula occurs in 1% to 2% of patients after neck dissection, especially when level IV nodes are dissected. Chylous fistula is often located in the lower left portion of the neck, so this characteristic location helps raise the suspicion of this complication. It is important to distinguish a benign fluid collection from an abscess or tumor recurrence. Early surgical complications such as serous retention, abscess, hematoma, and chylous fistula often show imaging findings similar to those of a fluid collection, with peripheral enhancement at CT and MR imaging. Clinical symptoms, such as fever, pain, and swelling, and laboratory parameters, such as a leukocytosis and elevated C-reactive protein level, can be used in distinguishing an abscess from other types of fluid collections.

Mucosal Necrosis

Mucosal necrosis is an uncommon but important late toxic effect of head and neck radiation therapy that may cause substantial pain and interferes with the patient's ability to chew and swallow. The risk for mucosal necrosis is greatest during the first 6 to 12 months after radiation therapy. In more than 95% of cases, soft tissue necrosis heals spontaneously, but healing may take 6 months or more or require hyperbaric oxygen therapy. Mucosal necrosis is a separate entity from acute mucositis; the latter results from an acute loss of functional cells and temporary lack of replacement from the pools of rapidly proliferating cells. If the reaction is severe, subsequent fibrosis occurs and leads to impairment of microvascular and lymphatic flow. This impairment produces hypoxic, hypocellular, and hypovascular tissue that is unable to maintain normal tissue turnover, resulting in mucosal necrosis and ulceration.

On CT and MR imaging, mucosal necrosis shows a lack of mucosal enhancement with breech of the mucosa and air dissecting submucosally with or without ulceration (Fig. 5.41). Pockets of gas identified adjacent to the lesion should raise concern for necrosis. Gas is more readily identifiable on CT compared with MR imaging. If the ulceration is associated with adjacent enhancement, the differentiation between radiation necrosis and recurrent tumor becomes difficult (Fig. 5.41). FDG-PET imaging often reveals hypermetabolism associated with areas of ulceration, which should not be mistaken as an absolute sign of recurrence (Figs. 5.45 and 5.52). Tumor recurrence and mucosal necrosis typically occur within 2 years after therapy,

so the time of the onset is less useful in distinguishing between radiation-induced injury and tumor recurrence. Mucosal complications are more easily diagnosed with the findings from clinical examination than with imaging but are not always clinically clear, and correlation with findings from clinical examination and close interval follow-up are necessary.[112,113]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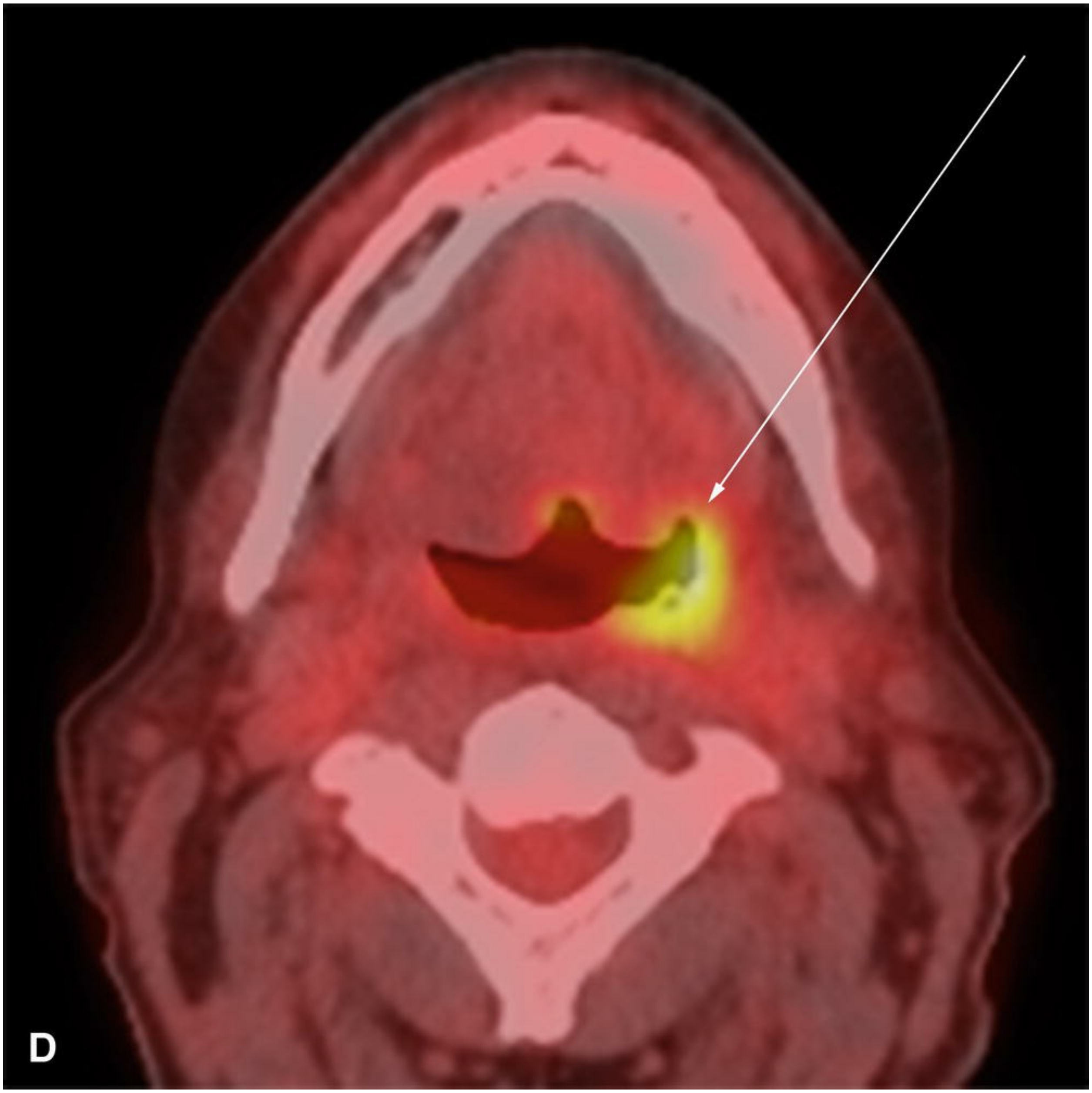
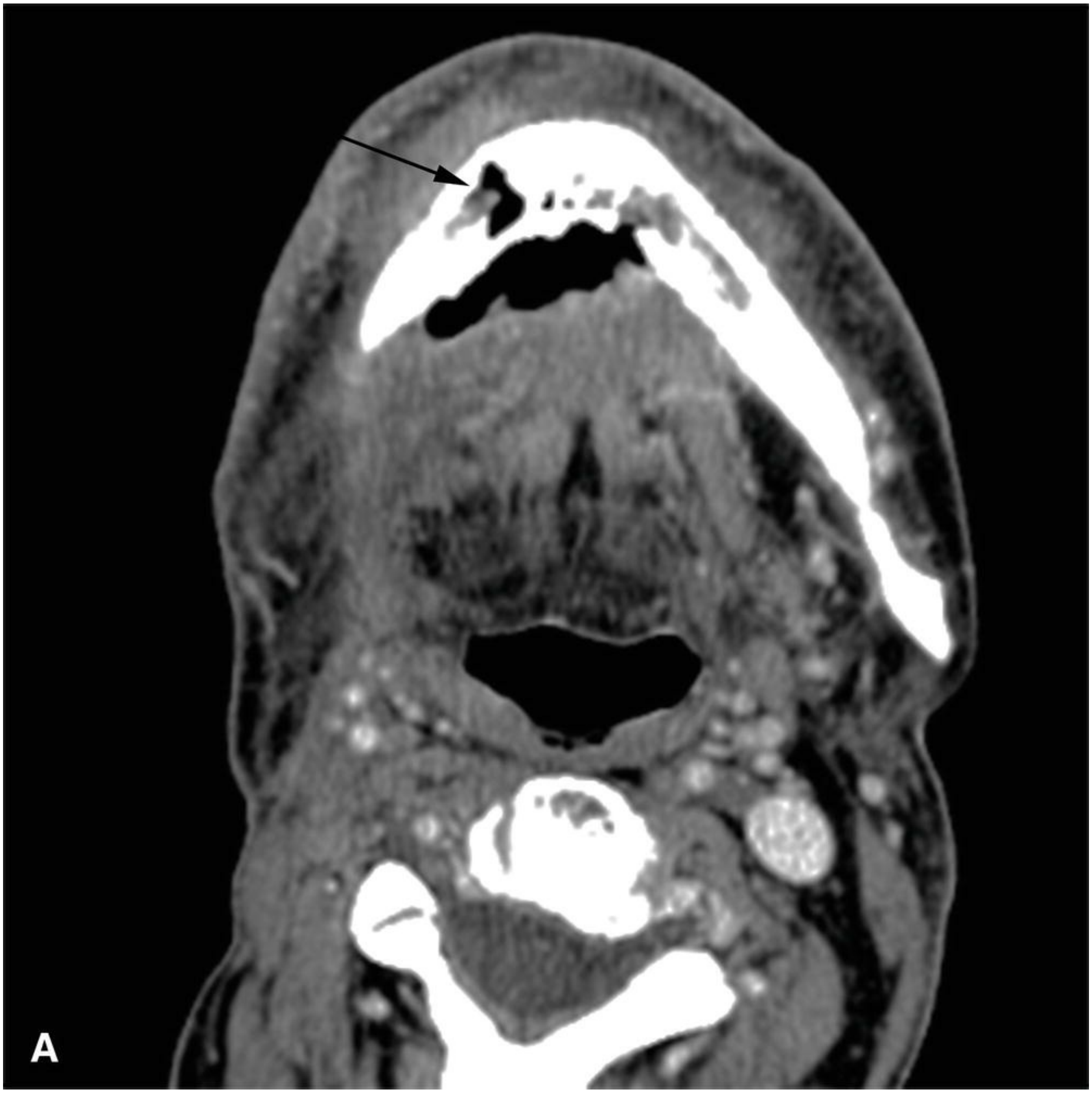


Figure 5.45. Postoperative mucosal changes including ulceration are common and can be difficult to differentiate from recurrent disease. In this 49-year-old man with squamous cell carcinoma of the left tonsil treated with chemoradiation and left neck dissection, posttreatment CT of the neck **(A)** 2 years following treatment shows an unremarkable appearance of the left oropharynx. A follow-up CT of the neck **(B)** with contrast 3 months later revealed development of nonenhancing ulceration (*arrow*), which was negative for locally recurrent disease. Similar findings are seen in this 53-year-old man with HPV-associated T3 squamous cell carcinoma of the left base of the tongue who was treated with chemoradiation. In this example, we

see **(C)** a similar appearing nonenhancing ulceration in the left oropharynx (*arrow*), which also displayed **(D)** hypermetabolism on FDG-PET/CT. This was later also proven to be negative for recurrence. Nonenhancement of an ulceration strongly argues against recurrent tumor.

Fistula

A fistulous tract is an abnormal pathway between an internal cavity or organ and the surface of the body. These may be caused by infection, tumor, radiation, or flap necrosis. Orocutaneous fistulas are not common, but may occur as a consequence of osteoradionecrosis (Fig. 5.46; see below). An orocutaneous fistula may lead to the continual leakage of saliva from the oral cavity to the face. Tumor can be difficult to exclude when fistulas are identified with adjacent enhancing soft tissue. Fistulas may close spontaneously, but some may require reoperation. Postoperative anemia, prior tracheotomy, and prior radiation therapy and neck dissection are associated risk factors for fistula formation. The severity and the duration of fistulas are greater in patients who have undergone prior radiation therapy than in those who have not.[112]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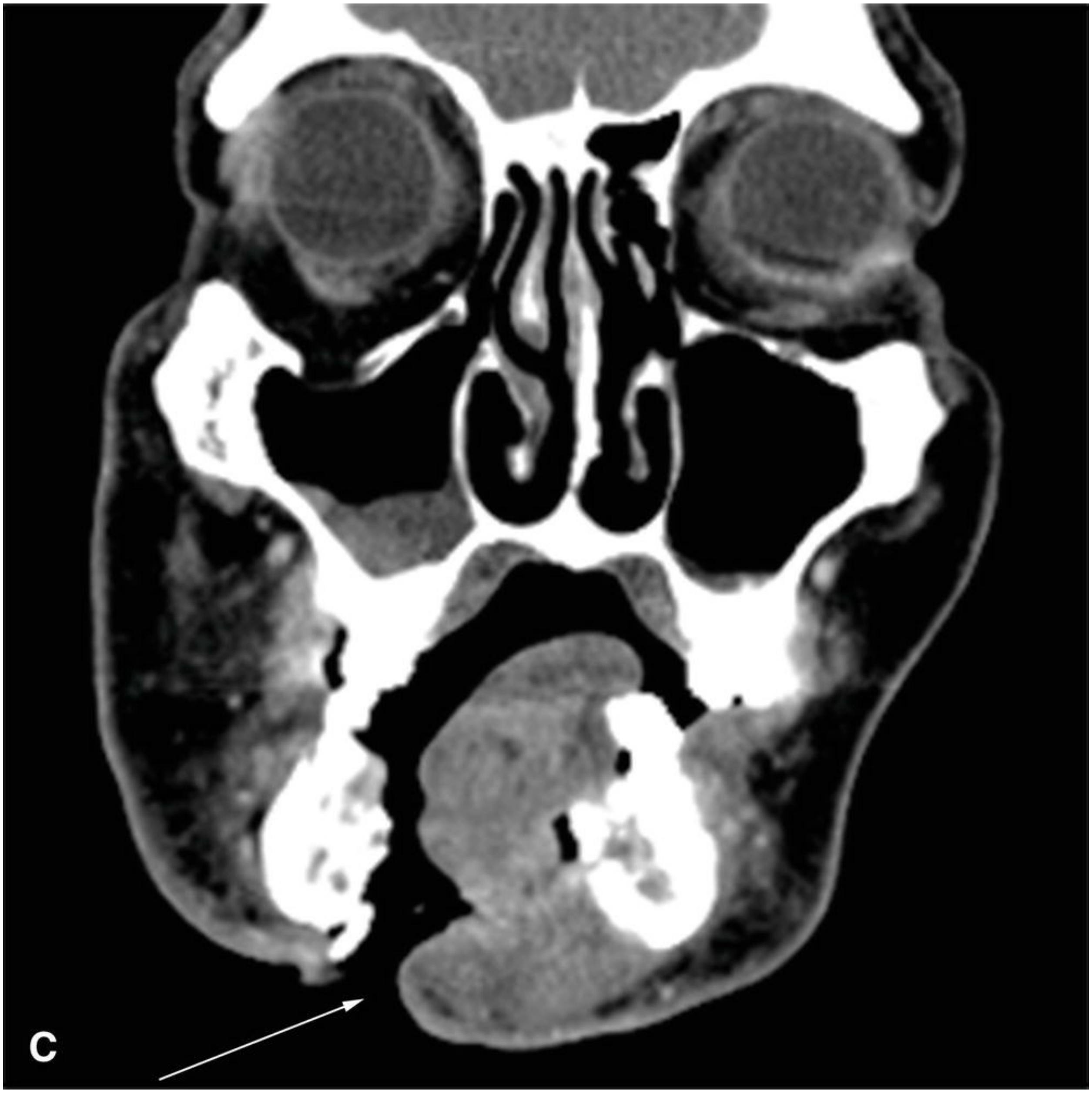
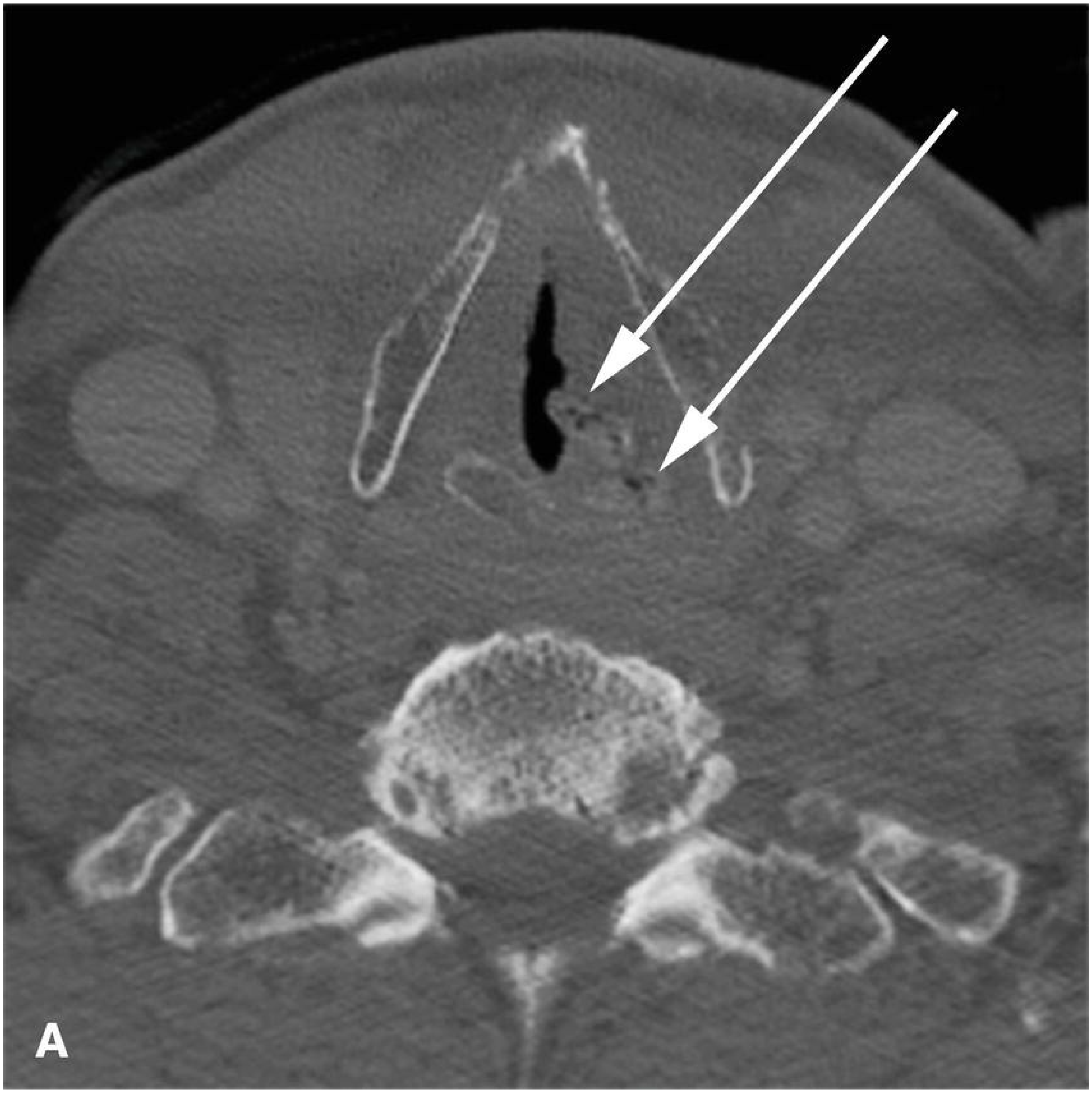


Figure 5.46. A 58-year-old man with squamous cell carcinoma of the right lateral tongue status post wide local excision, right neck dissection, and radiation therapy. **A:** A CT of the neck with contrast in soft tissue windows reveals intraosseous air in the mandibular marrow space (*arrow*). **B:** Bone windows better reveal irregular lytic changes within the mandible, compatible with osteoradionecrosis. The cortical disruption of the pathologic fracture is seen on this image (*arrow*). **C:** A coronal reconstructed image of the CT of the neck reveals orocutaneous fistula to the submental region (*arrow*).

Osseous Complications

The exact definition of osteoradionecrosis is variable, but in general, it is a condition in which irradiated bone becomes devitalized and exposed through the overlying skin or mucosa, persisting without healing for at least 3 months. The reported incidence of osteoradionecrosis varies greatly in the literature, ranging from 0.4% to 22% in patients with head and neck cancer, and generally occurs within several years of radiation therapy (XRT).

Osteoradionecrosis is unlikely to occur if the radiation dose, delivered by standard fractions, is below 60 Gy. There is a higher likelihood of occurrence if the dose is higher than 65 to 75 Gy. Sites that can be affected by osteoradionecrosis in the head and neck region are the skull base, temporal bone, mandible, maxilla, and hyoid bone. The mandible is the most common site of osteoradionecrosis related to its superficial location and relatively poor blood supply (Fig. 5.46). The symptoms of osteoradionecrosis in the head and neck region are chronic focal pain, swelling, and facial deformation. In the case of the mandible, common signs and symptoms include dysphagia, drainage, and fistulization to the mucosa or skin. Laryngeal chondronecrosis can be considered a subtype of radionecrosis and is manifested clinically by dysphagia, odynophagia, respiratory obstruction, hoarseness, and aspiration (Fig. 5.47). The vast majority of patients develop symptoms within 1 year of treatment, but significantly delayed presentations of up to 25 years have been reported.[114]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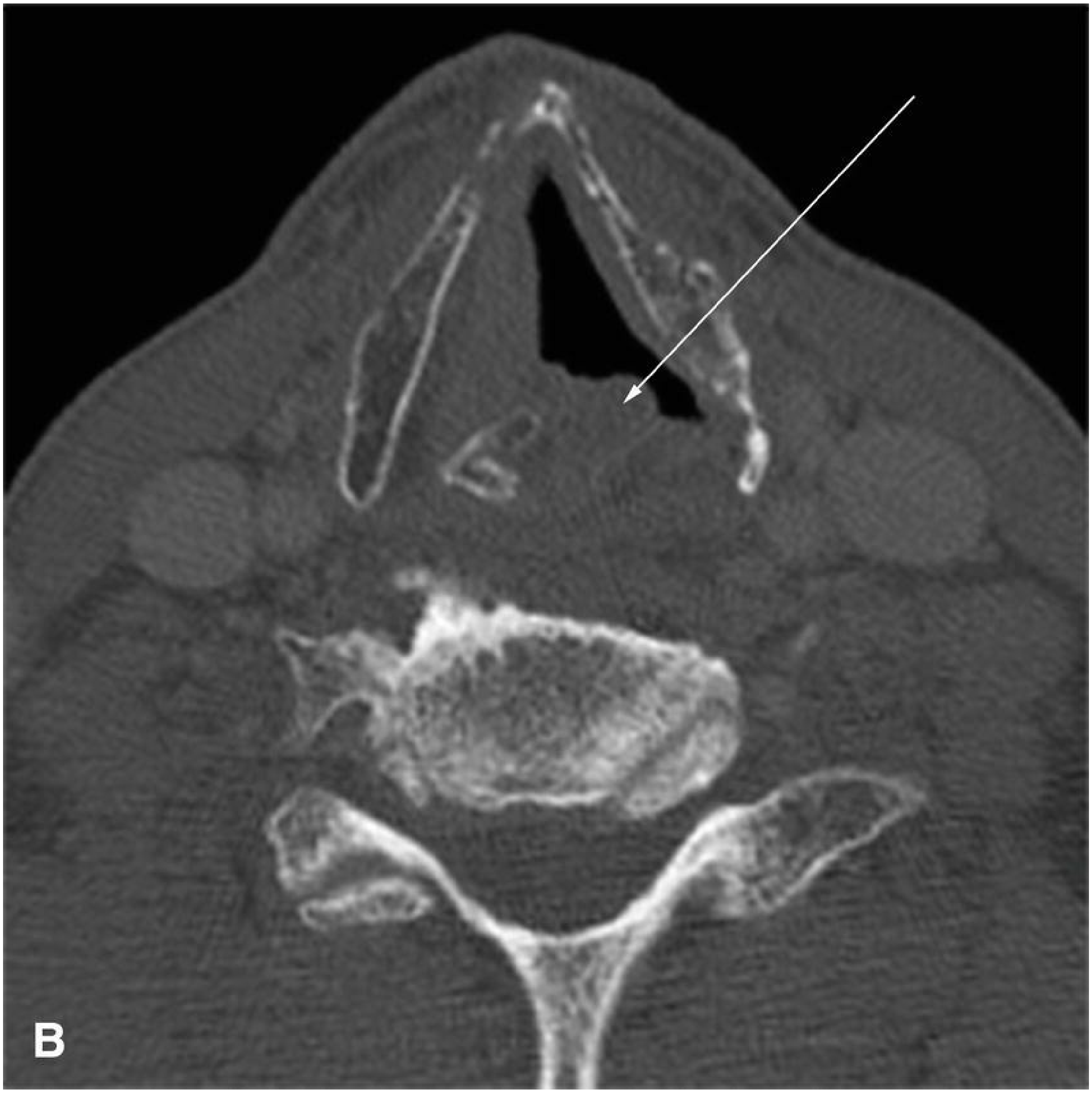
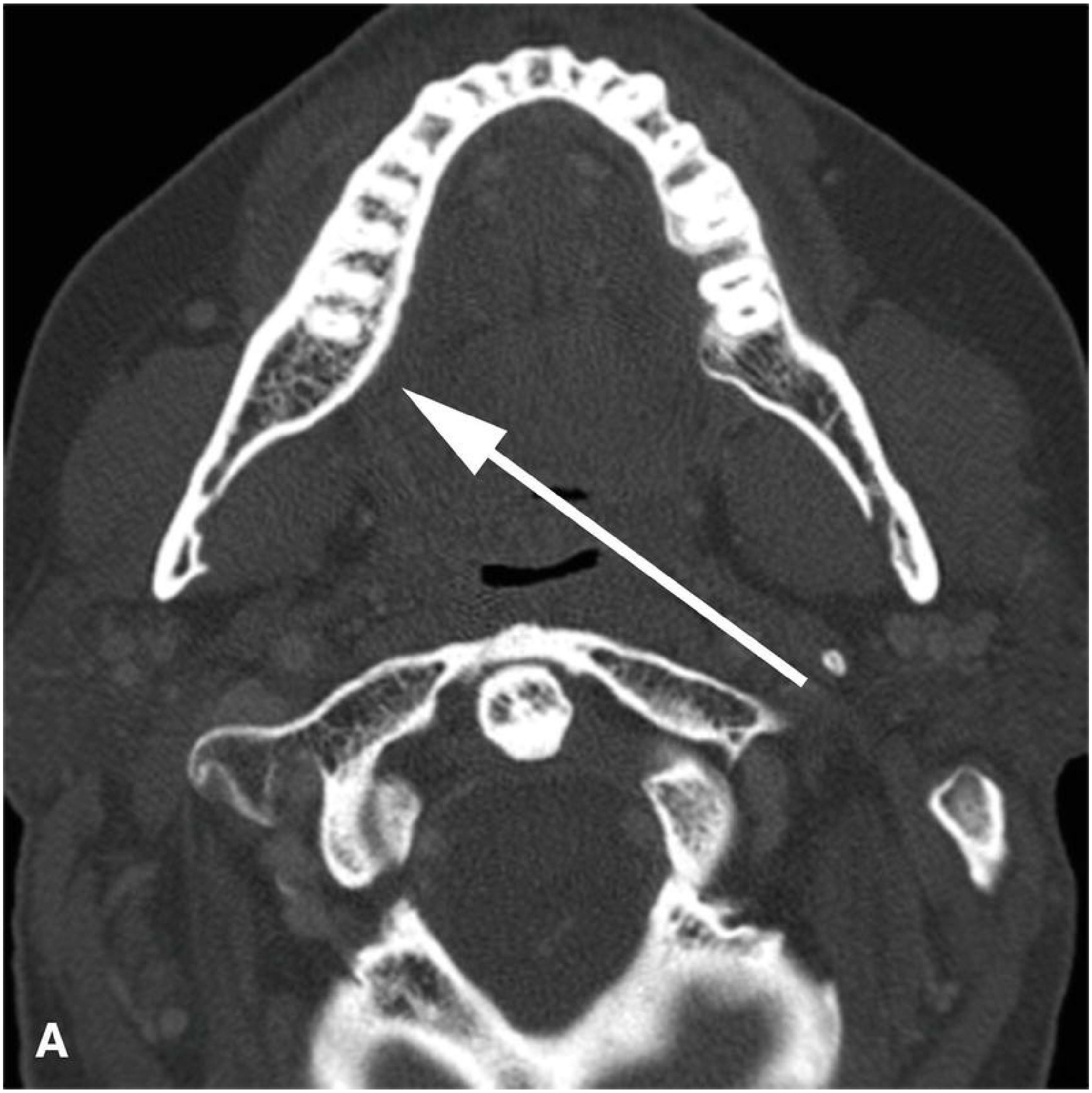


Figure 5.47. A 56-year-old man with a T2 squamous cell carcinoma of the right true vocal cord treated with radiation therapy subsequent development of chondroradionecrosis of the left arytenoid. CT of the neck with contrast in bone window **(A)** reveals small foci of air within a poorly outlined left arytenoid cartilage (*arrow*). Subsequent imaging **(B)** reveals autoamputation of the left arytenoid (*arrow*). The normal right arytenoid is well seen on this image.

Osteoradionecrosis typically displays as a well-defined lytic region with cortical destruction, sequestrum formation, and loss of normal trabeculation

pattern. An early imaging finding is loss of lingual mandibular cortical bone (Fig. 5.48). MR images of osteoradionecrosis show abnormal signal intensity in the bone marrow, though the associated cortical disruption may be inapparent. Pathologic fracture, soft tissue thickening, and fistula formation are sometimes seen. Although these imaging findings can mimic those of tumor recurrence, the presence of an associated soft tissue mass favors a diagnosis of tumor recurrence. The identification of cortical defects remote from the primary tumor site can also help in the diagnosis of osteoradionecrosis. Synchronous or metachronous lesions can occur in cancer patients, but are rare, progressively destructive, and typically have an enhancing soft tissue component.[115]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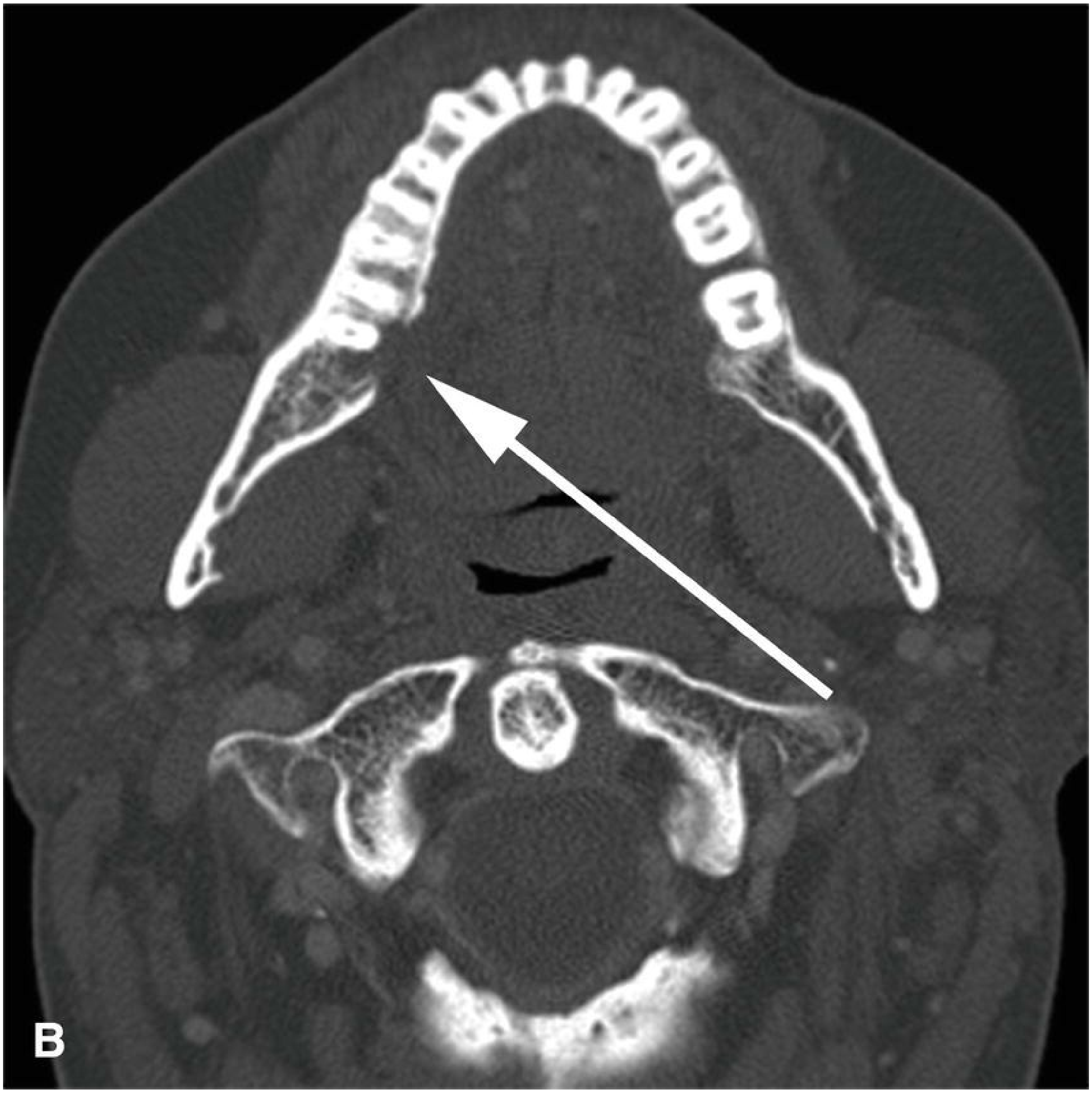
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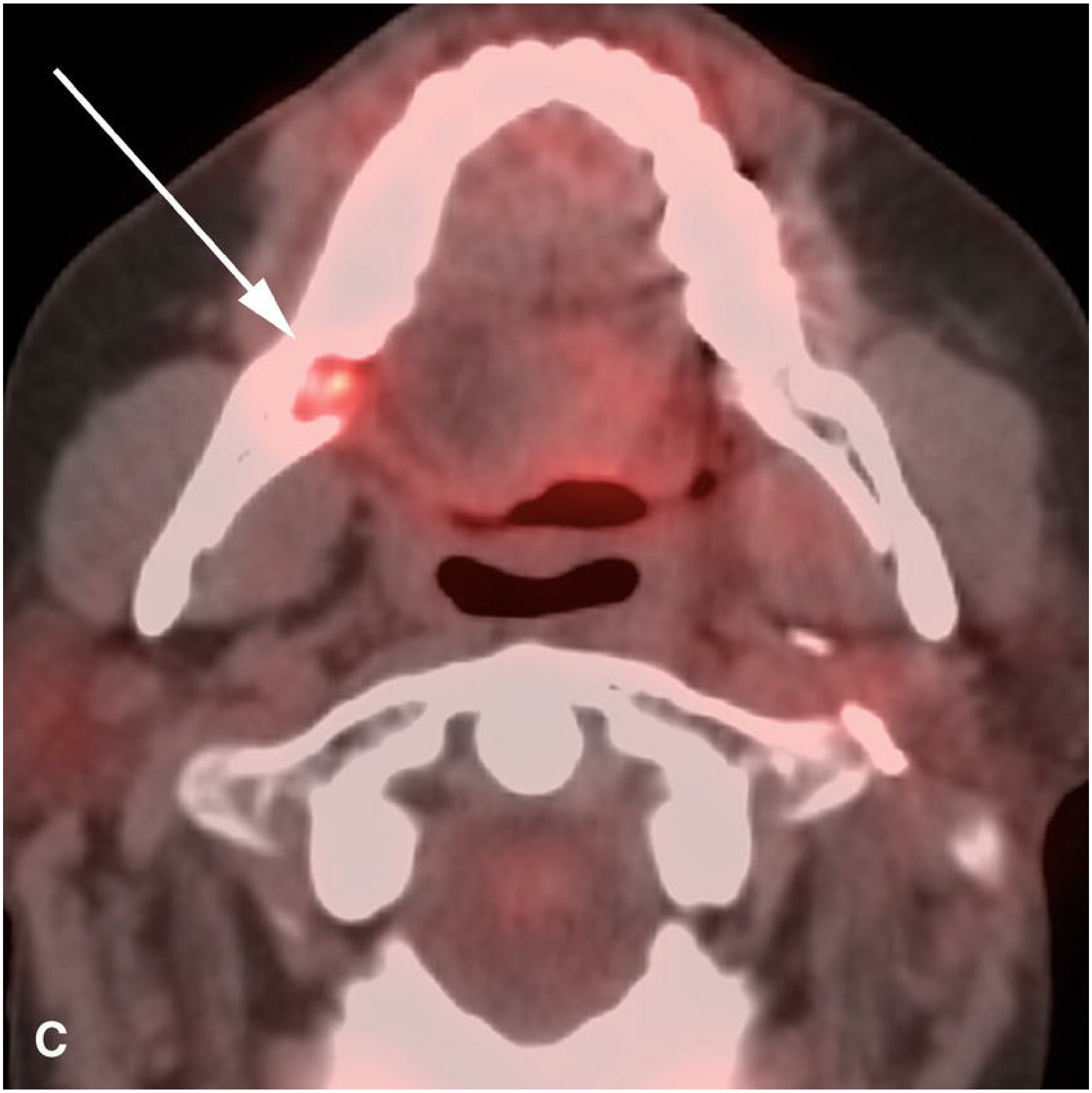


Figure 5.48. A 56-year-old man with T2 N2C squamous cell carcinoma of the left base of the tongue treated with chemoradiation and subsequent development of osteoradionecrosis of the mandible. **A:** Baseline postradiation CT of the neck with contrast in bone window shows a normal appearance of the right mandibular lingual cortex (*arrow*). **B:** Imaging 16 months following treatment reveals a lingual cortical defect in the right mandible (*arrow*), which was also noted to be hypermetabolic on FDG-PET/CT. **C:** The degree of hypermetabolism, although not striking, could be misinterpreted as tumor without CT and clinical correlation.

Vascular Complications

Accelerated atherosclerosis and thrombosis of the internal jugular vein or carotid artery are well-known vascular complications in patients with radiation therapy. Formation of a pseudoaneurysm of the internal carotid artery is reported to be a rare complication after radiation therapy. Radiation-induced vasculopathy occurs most often in patients who have undergone high-dose radiation therapy, with a latency period between 4 months and 20 years. However, most patients treated for head and neck cancer have preexisting ischemic vascular disease secondary to alcohol and tobacco consumption and elevated serum cholesterol and lipid levels. The imaging findings of radiation-induced vasculopathy mimic those of other atherosclerotic disease and cannot be differentiated based on imaging findings alone. Radiation-induced vasculopathy is often bilateral and related to the irradiated field.[116]

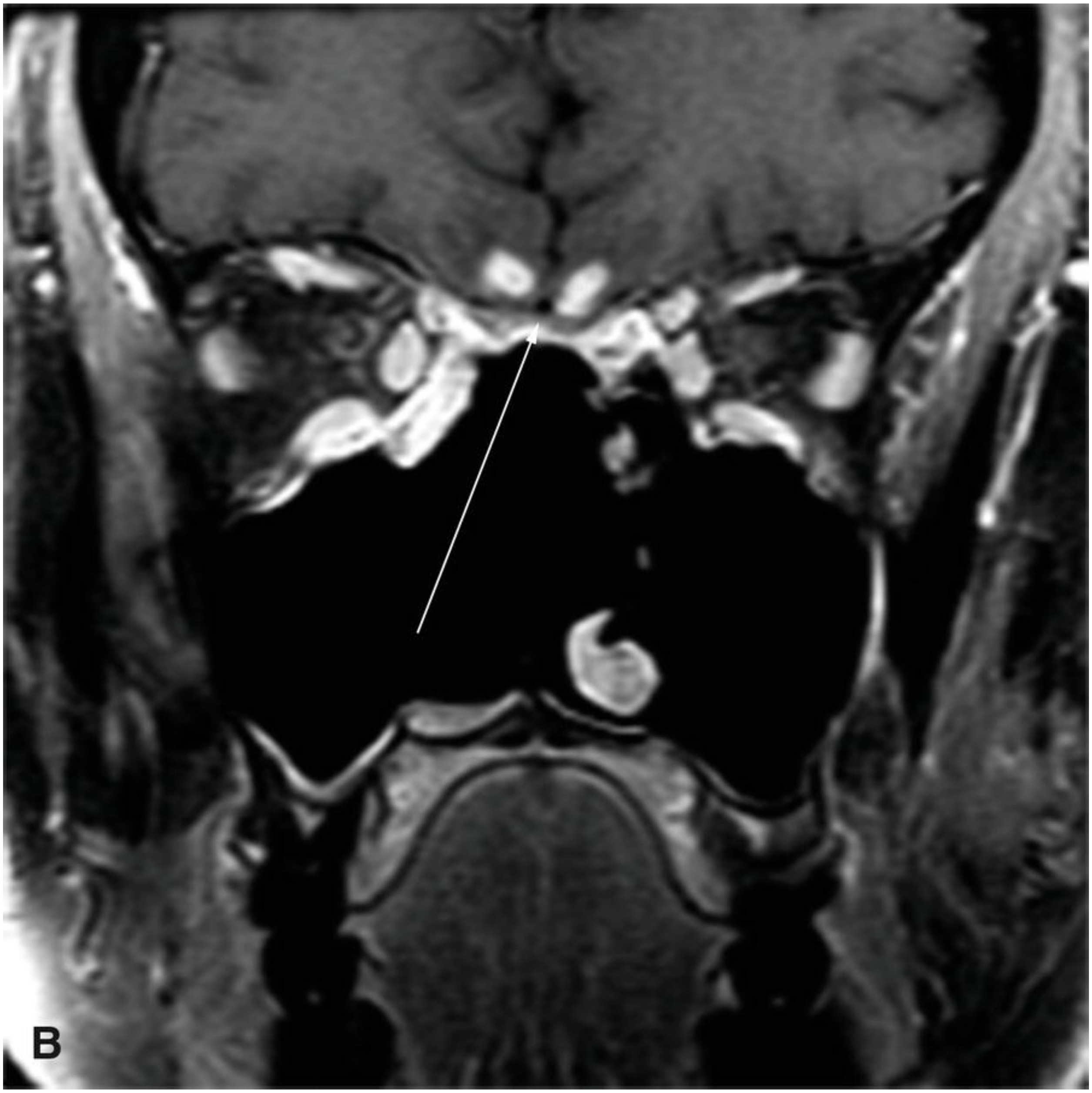
Radiation-Induced Lung Disease

Radiation therapy for patients with head and neck cancer often includes the apical aspect of the thorax, to encompass the supraclavicular nodes and level IV nodal areas, and results in bilateral apical radiation-induced lung changes. Clinically, these changes may manifest as acute radiation pneumonitis or late radiation lung fibrosis. Radiation pneumonitis occurs within 1 to 3 months after completion of radiation therapy, and radiation fibrosis occurs within 6 to 12 months after radiation therapy and can progress for as long as 2 years before stability occurs. Radiation pneumonitis appears as focal ground-glass attenuation and/or consolidation. Radiation pneumonitis gradually resolves but can progress to fibrosis if the damage is severe. Radiation lung fibrosis is shown to be a well-defined area of volume loss, linear scarring, and traction bronchiectasis.[117]

Radiation-Induced Brain Necrosis

Radiation-induced brain necrosis often occurs within 2 years after radiation therapy. Irradiation of skull base or external ear/other cutaneous tumors may result in radiation damage to adjacent brain tissue. Radiation therapy in patients with nasopharyngeal cancer is associated with temporal lobe necrosis in ~3% of patients. This condition was previously seen more commonly with

older irradiation techniques. The incidence of temporal lobe necrosis with intensity-modulated radiation therapy is now markedly lower because the brain is contoured as an avoidance structure and because maximal doses are maintained at <60 Gy. Focal brain necrosis can present as an enhancing mass with variable edema on imaging, often beginning as small, spotty areas of enhancement. An actual mass may come later if at all (Fig. 5.49). The knowledge of prior definite head and neck radiation along with the typical location involving the medial anterior temporal lobe should be sufficient in most patients to confidently make this diagnosis with imaging alone.[118]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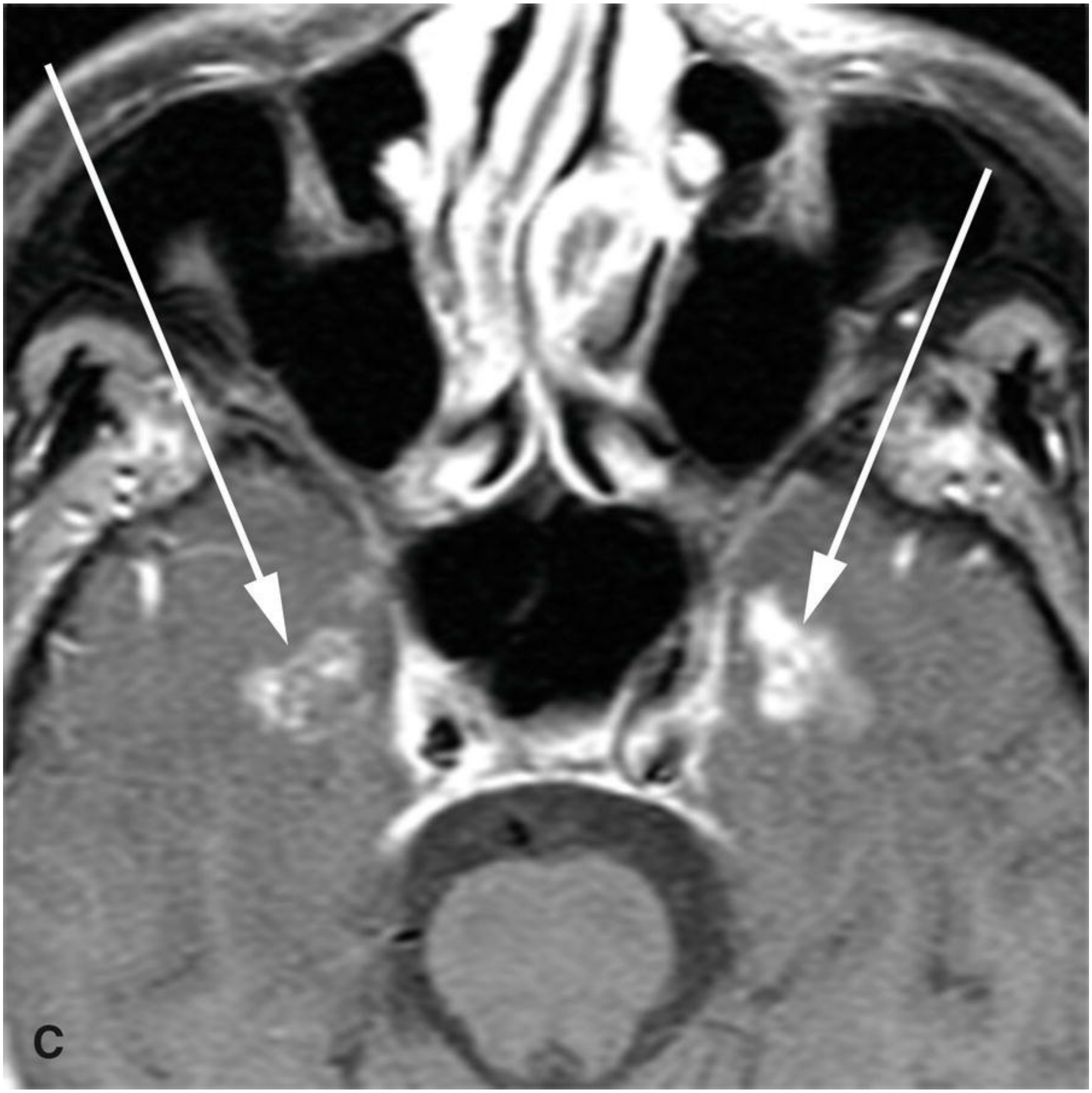


Figure 5.49. Cerebral radiation necrosis can have features suggestive of a primary brain neoplasm although it tends to occur in predictive sites following radiation treatment to the head and neck. In this 40-year-old man with sinonasal undifferentiated carcinoma treated with surgery and radiation, characteristic findings of cerebral radiation necrosis developed ~2 years after radiation completed. Axial **(A)** and coronal **(B)** T1-weighted postcontrast MR images of the brain reveal bilateral and relatively symmetric enhancing lesions (*arrow*) without mass effect in the gyrus rectus anteriorly. In this **(C)** 49-year-old man with T4 nasopharyngeal carcinoma treated with chemoradiation, there are similar findings on postcontrast T1-weighted MR

imaging although this time the lesion is seen within the bilateral medial anterior temporal lobes (*arrows*).

Radiation-Induced Neoplasm

Radiation-induced neoplasm is rare, with one group of investigators reporting an incidence rate of 0.04% for postirradiation sarcoma in patients who had undergone treatment for nasopharyngeal cancer. These investigators reported that the latency period ranged between 4 and 27 years. Various types of radiation-induced neoplasms have been reported, including meningioma, sarcoma (osteosarcoma, malignant fibrous histiocytoma), osteochondroma, schwannoma, osteoblastoma, SCC, and lymphoma. The diagnostic criteria of postirradiation osteosarcoma include a lesion centered in irradiated bone without a primary malignant osteoblastic lesion, arising after a latency period of at least 3 years after the completion of radiation therapy (Fig. 5.50). Imaging findings mimic those of primary osteosarcoma.[119]


A

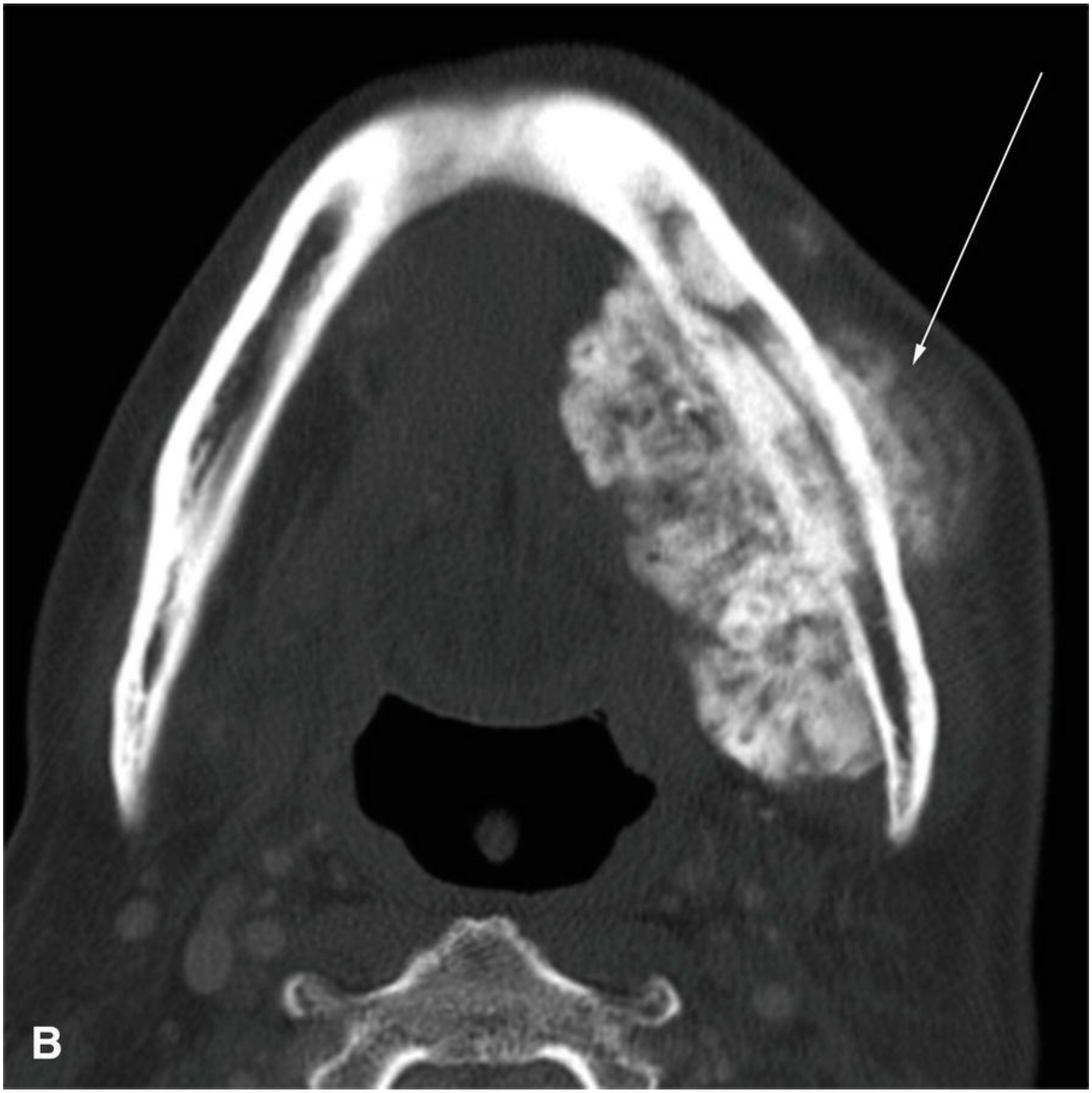


Figure 5.50. A 48-year-old man who originally presented with carcinoma of the left submandibular gland treated with resection and brachytherapy. Regional recurrent disease was later treated with neck dissection and radiation therapy. Approximately 7 years after original presentation, the patient developed a mass arising from his left mandible, which was biopsy-proven osteoblastic osteosarcoma arising within the radiation field. A CT of the neck in soft tissue **(A)** and bone window **(B)** reveals a bone-producing mandibular mass (*arrow*) arising from the left mandible with enhancing soft tissue along the margins (*arrow*).

Posttreatment Surveillance Imaging

As discussed earlier, the typical imaging modalities used for posttreatment surveillance include CT, US, MRI, and FDG-PET/CT. Imaging plays an important role in the early detection of recurrence, to allow early intervention and salvage treatment. The combination of clinical endoscopic and physical examination coupled with imaging is geared toward the early detection of recurrence (Fig. 5.51).

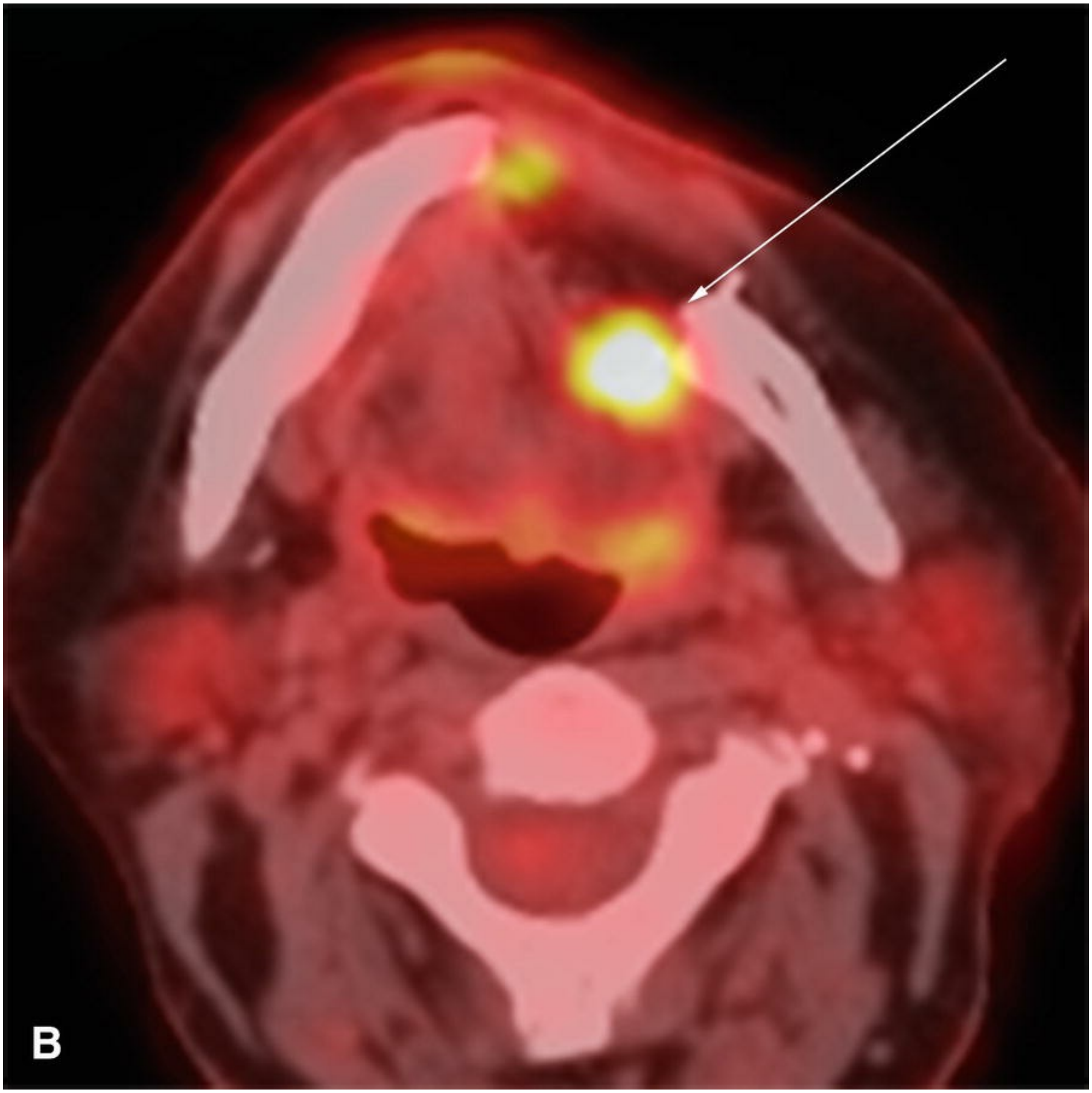
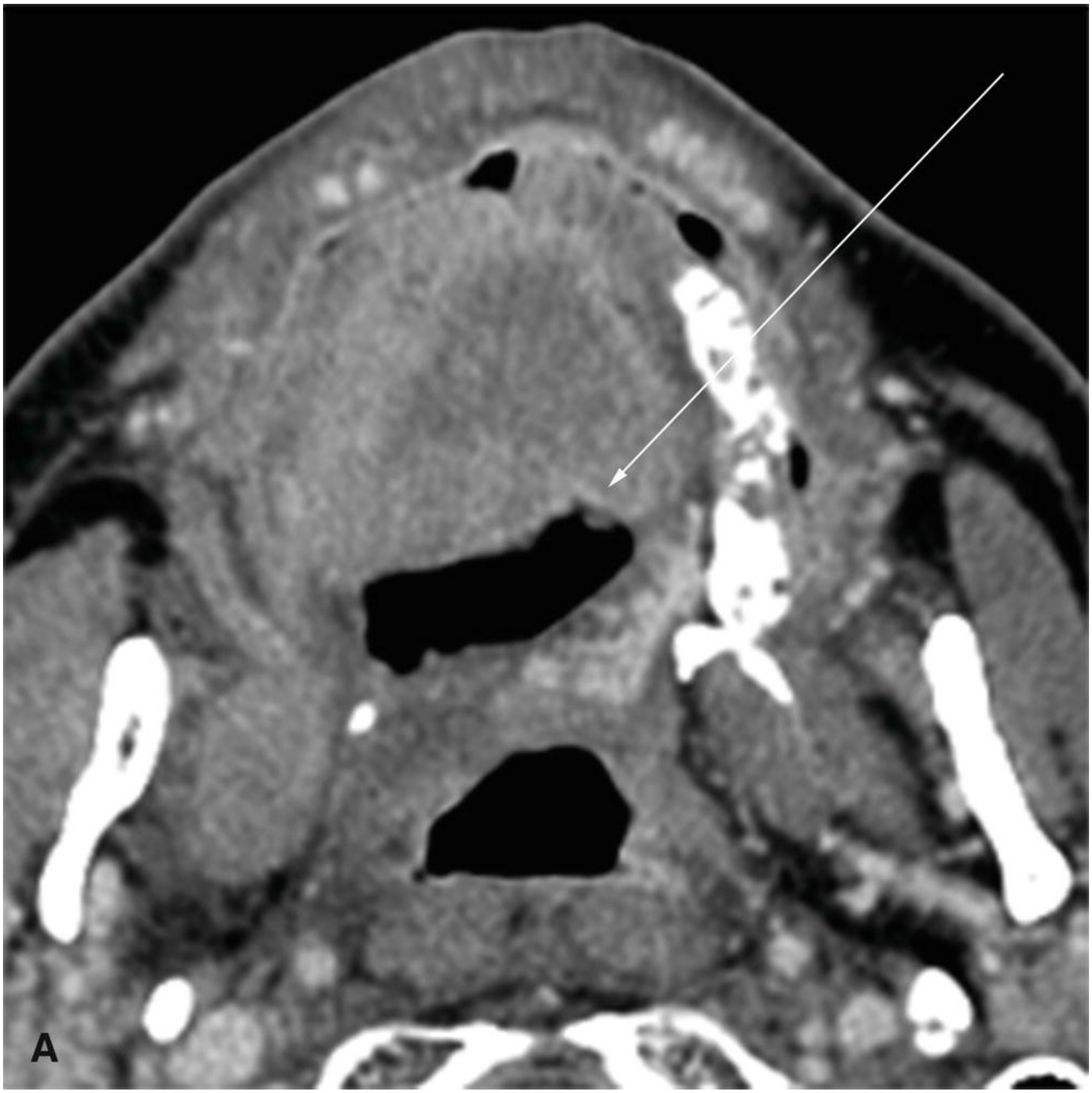


Figure 5.51. A 68-year-old-male with a squamous cell carcinoma of the left floor of mouth treated with resection, neck dissection, and flap reconstruction. Surveillance CT of the neck with contrast **(A)** and FDG-PET/CT **(B)** 3 months after surgery revealed findings of subsequent proven recurrent disease in the left anterior floor of the mouth (*arrow*).

The acquisition of a baseline imaging examination is important to serve as a reference for evaluation in the posttreatment follow-up. Surgery alters the normal anatomy, tissue planes, and landmarks in the head and neck. Radiation treatment induces tissue distortion including edema, late

microvascular injury, and fibrosis. These posttreatment changes can make it difficult to distinguish expected treatment-induced changes from tumor recurrence or complications. The baseline imaging examination should optimally be performed at the time when most postoperative changes have resolved and when tumor recurrence rarely occurs. A baseline examination with CT or MR imaging can be performed between 8 and 10 weeks after treatment (Fig. 5.52).



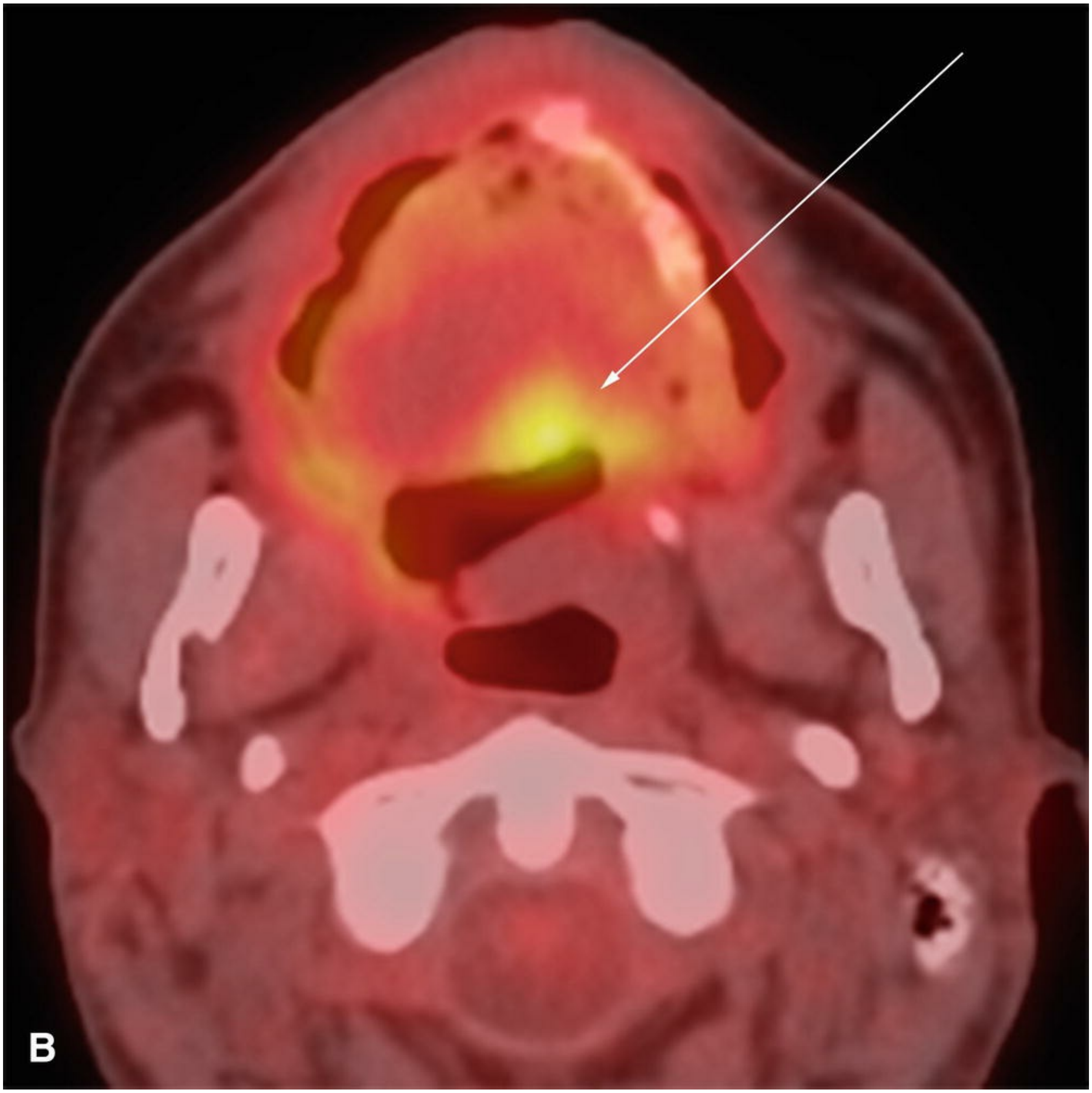


Figure 5.52. A 48-year-old man 2-month status post chemoradiation for oropharyngeal carcinoma was found to have a nonenhancing shallow ulceration along the left tongue base on **(A)** CT of the neck with contrast that was also noted to be hypermetabolic **(B)** on an FDG-PET/CT performed the same day (*arrow*). Continued surveillance showed resolution of this finding consistent with radiation-induced ulceration. It should be kept in mind that FDG avidity is typical in benign ulcerations and does not in and of itself suggest malignancy.

The imaging technique used for the baseline or surveillance examination

is often determined based on the primary site and stage. CT is widely used for follow-up because of its rapid image acquisition and adequate coverage of the cervical nodal basins. MR imaging, given its superior soft tissue contrast, is sometimes preferred for patients with sinonasal, salivary gland, nasopharyngeal, and skull base tumors. Although there is not widespread consensus on the frequency of surveillance, at many institutions, it is performed every 3 to 4 months in the first 2 years, every 4 to 6 months during years 2 to 5, and annually thereafter.

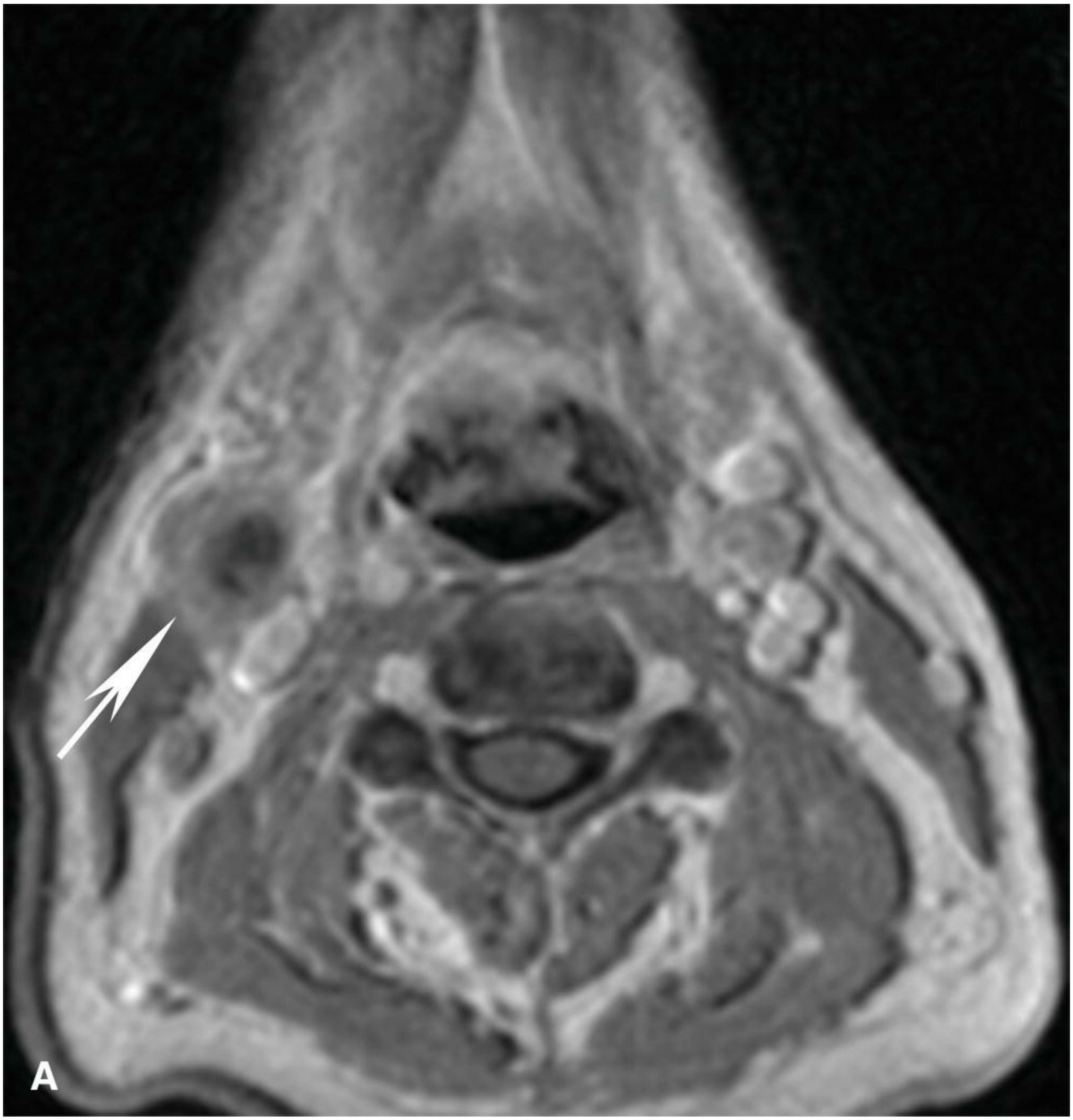
EMERGING IMAGING TECHNIQUES FOR EVALUATION OF HEAD AND NECK CANCER AND CONCLUSIONS

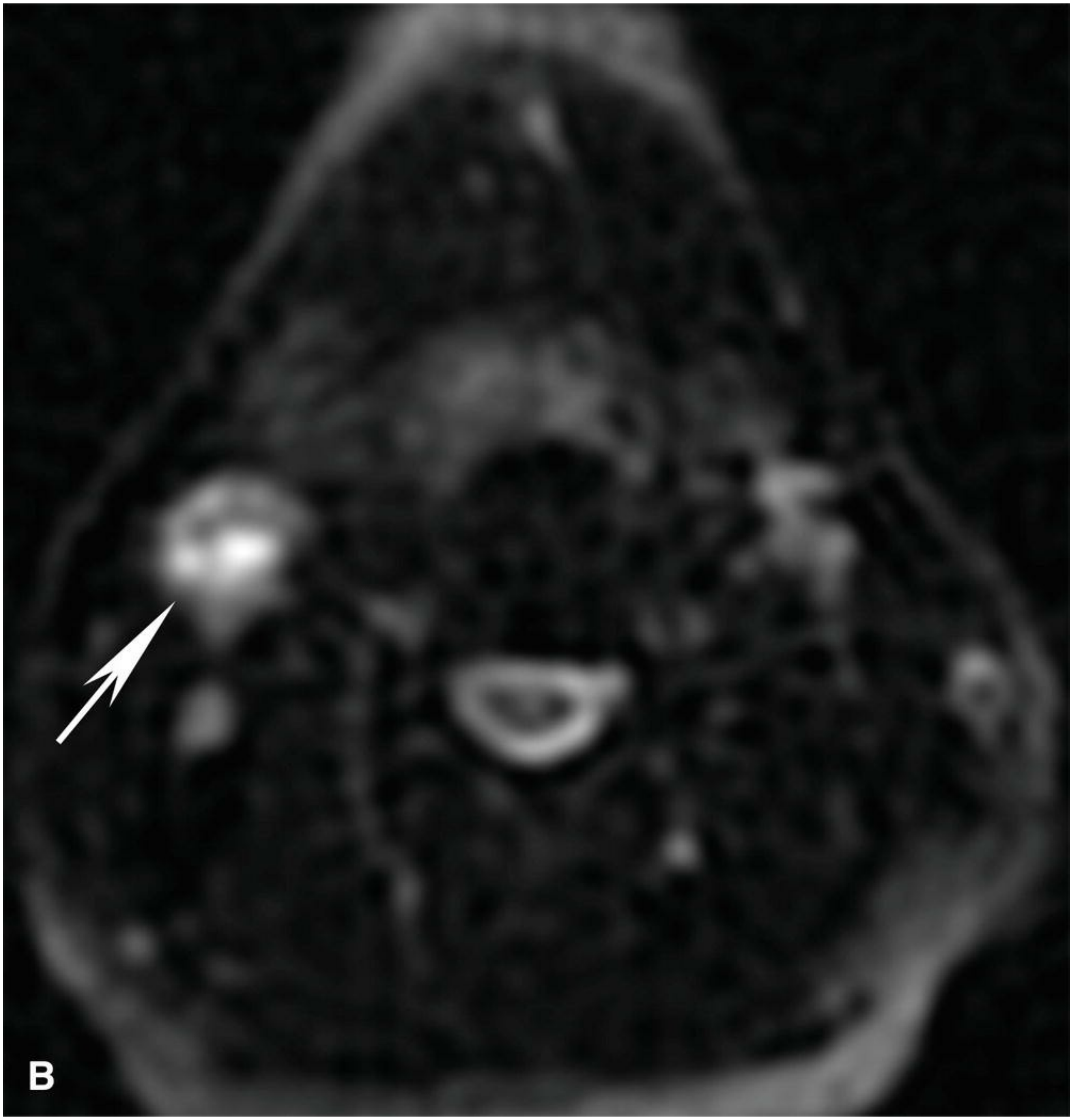
Emerging Imaging Techniques for Evaluation of Head and Neck Cancer

Diffusion-Weighted MR Imaging

Diffusion-weighted magnetic resonance imaging (DWI) is a technique used to evaluate the diffusion of water molecules in tissues with applications to a wide array of pathologic conditions.[120] DWI is widely used in brain imaging and is the most reliable imaging method for evaluation of acute brain ischemia. However, there are additional potential applications of DWI, including in imaging of tumors. When evaluating tumors, the basic principle behind DWI is that tissues with higher cellularity form a greater barrier to water diffusion compared to less cellular tumors.[120–123] A detailed discussion of the DWI imaging and specific maps generated is beyond the scope of this chapter. However, in general, malignant tumors tend to demonstrate greater restriction/barrier to water diffusion, reflected in a lower measured value of the ADC map. In addition to primary tumor, DWI has been used for evaluation of lymphadenopathy (Fig. 5.53), to predict prognosis, and to evaluate tumor response, and the initial results are encouraging.[121–126] One pitfall of DWI is that even though the trends between tumor and benign tissues are different, there can be significant overlap between individually measured ADC values. Quantitative mapping has the potential to improve

accuracy, but incorporation into routine clinical practice is a challenge that would have to be overcome. It should also be noted that DWI can be technically challenging to optimize in the neck and can be limited in its spatial resolution. At this time, DWI is not in routine use, and the added value of the technique and incorporation in routine daily practice for evaluation of head and neck cancer requires further investigation and validation.




B

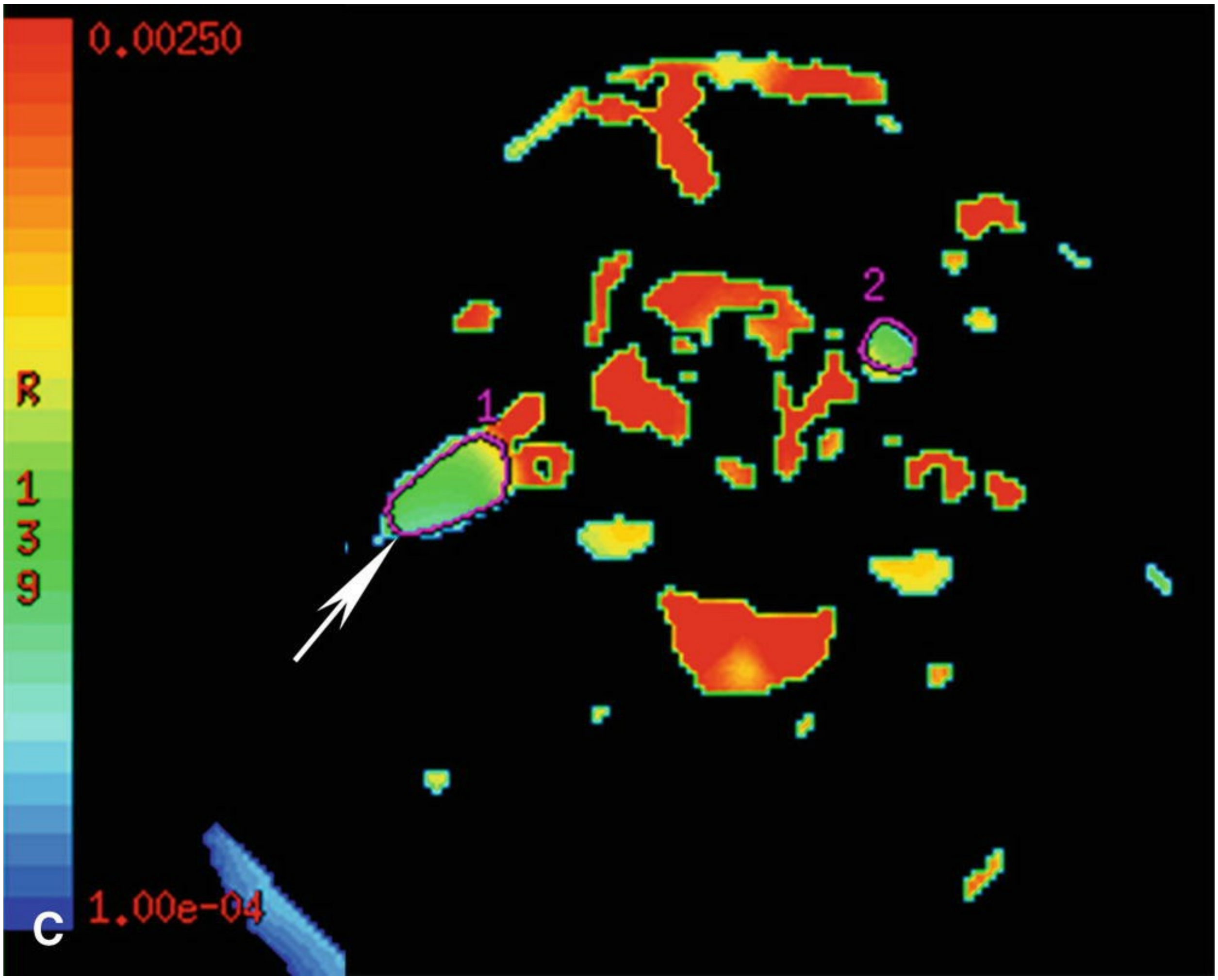


Figure 5.53. Diffusion-weighted imaging in head and neck cancer. Axial contrast-enhanced T1w **(A)** MRI image from a patient with a base of tongue cancer (not shown) demonstrates a pathologic right level II node (*arrow*). Standard **(B)** and color-coded ADC maps **(C)** (b = 500 mm/s^2) demonstrate areas of relative restriction (decreased ADC value) within the pathologic lymph node. On the standard ADC map shown in **(B)**, these appear as relatively dark areas intermixed with foci of high signal. On the color-coded map, the ADC value can be compared to other structures based on the color-coded scale provided on the left side. (Figures courtesy of Dr. A. Dmytriw.)

Dual-Energy Computed Tomography

Dual-energy CT (DECT) is a CT technique based on simultaneous or near-simultaneous acquisition of images at two different x-ray energies, enabling spectral evaluation of tissues and material tissue characterization beyond

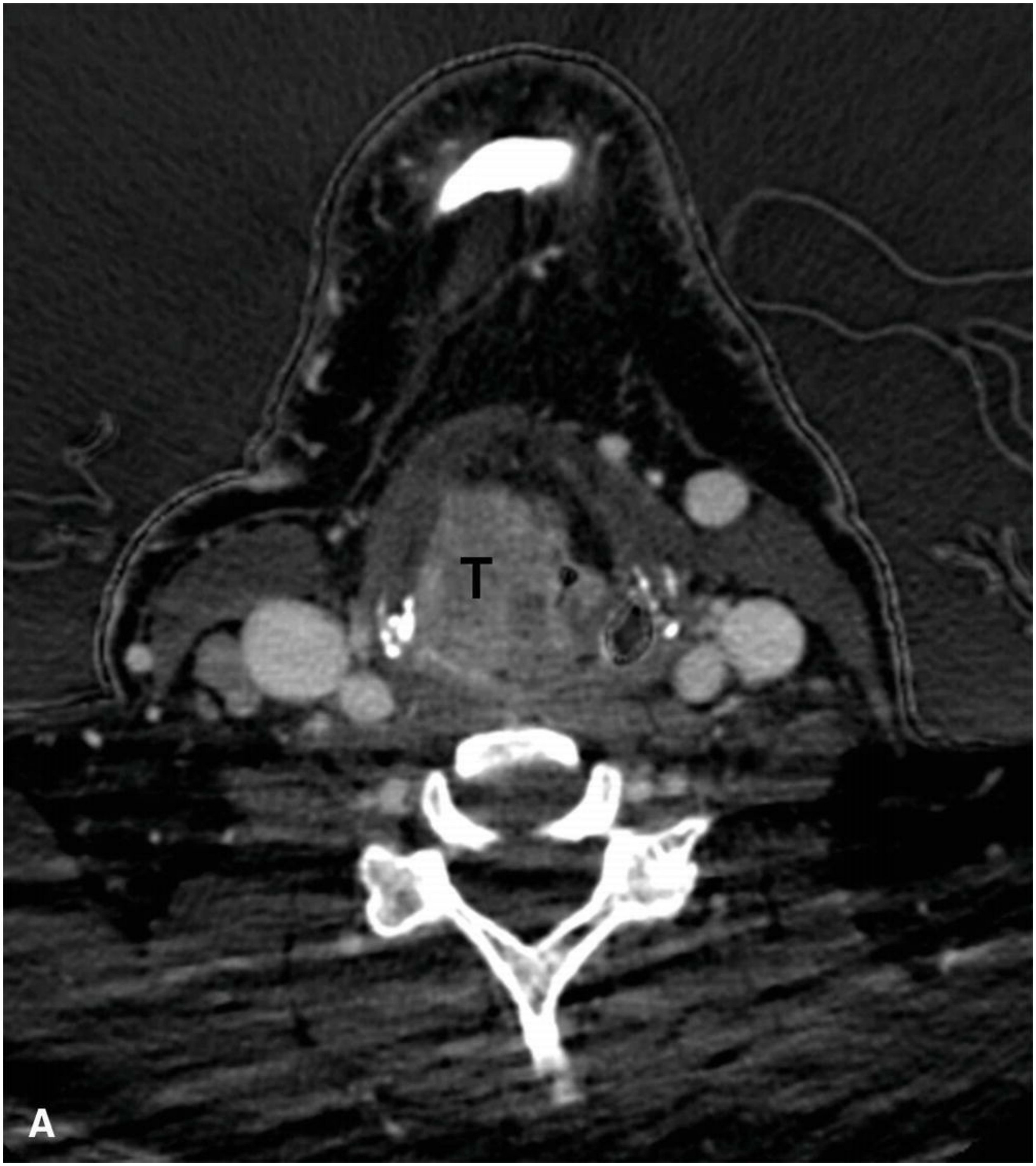
what can be done with a conventional CT scan.[127] There is emerging evidence that DECT may increase head and neck cancer tumor conspicuity, improve accuracy for determination of thyroid cartilage invasion, and may improve evaluation of areas degraded by artifacts due to dental fillings and implants.[96,128–139] In brief, scans acquired as a dual-energy scan can be processed to generate virtual monochromatic images (VMIs) and iodine maps, among other functionalities, for complementary evaluation of head and neck cancer.

VMIs are images reconstructed at different energy levels and can be used to accentuate different tissue characteristics. For example, lower energy VMIs accentuate iodine content and therefore can increase tumor conspicuity[132,134–137] (Fig. 5.54). Iodine overlay maps are color-coded maps that are mathematically extracted from the DECT data reflecting the iodine content of tissues and can be used to highlight the iodine content of enhancing tumor compared to background structures (Fig. 5.55). In one study, these have demonstrated to increase accuracy for determination of thyroid cartilage invasion.[128] In addition, nonossified thyroid cartilage has different characteristics than tumor on high-energy VMIs, and these reconstructions could also be helpful for the evaluation of thyroid cartilage[133] (Fig. 5.56). More advanced quantitative analysis can also be performed with DECT. As such, DECT is a promising technique for evaluation of head and neck cancer. However, it should be noted that DECT is not yet in widespread use and its added value requires further validation. Furthermore, for successful implementation into routine practice, it is important that the key reconstructions are automatically generated and readily available for interpretation.


T
A

Figure 5.54. Dual-energy CT (DECT) virtual monochromatic images (VMI) for increasing tumor conspicuity. DECT images from a patient with a right hypopharyngeal tumor (T) with lateral spread are shown. 70 keV VMI **(A)** (the energy level typically considered similar to conventional single-energy CT) and 40 keV VMI **(B)** of the same level are shown. The images are windowed similarly to provide a proper comparison (note the similar very

low dark density of subcutaneous fat). Note the increased conspicuity of the tumor and its margins on the 40 keV VMI **(B)** compared to the 70 keV VMI **(A)**.



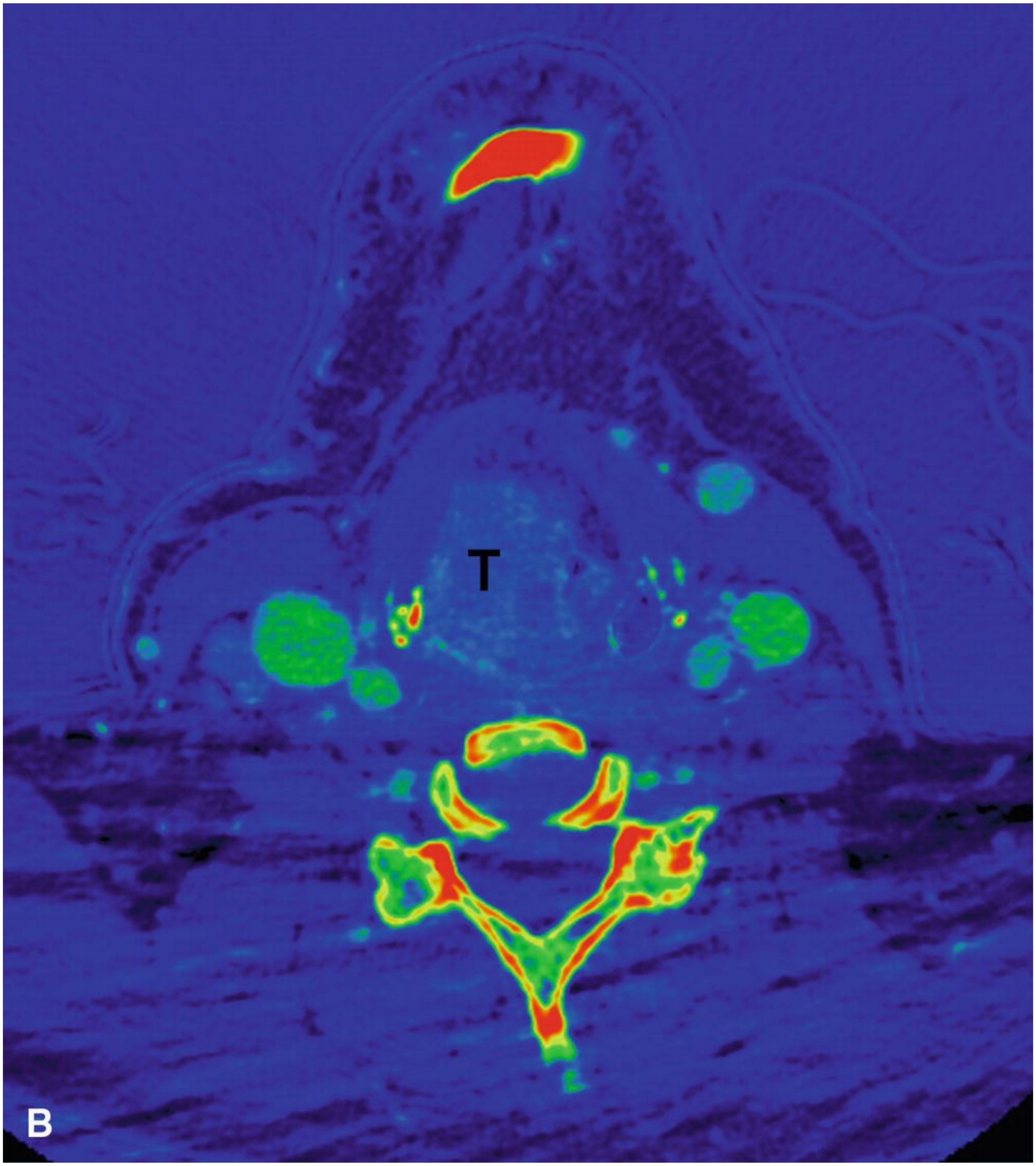


Figure 5.55. Dual-energy CT (DECT) iodine overlay maps. Iodine overlap map displayed in gray scale **(A)** and color **(B)** is shown from a patient with supraglottic squamous cell carcinoma (T). Note the increased iodine content of tumor (T), as reflected in the density/brightness, compared to muscles. As expected, the vessels have the greatest iodine content of the soft tissues.


T
A

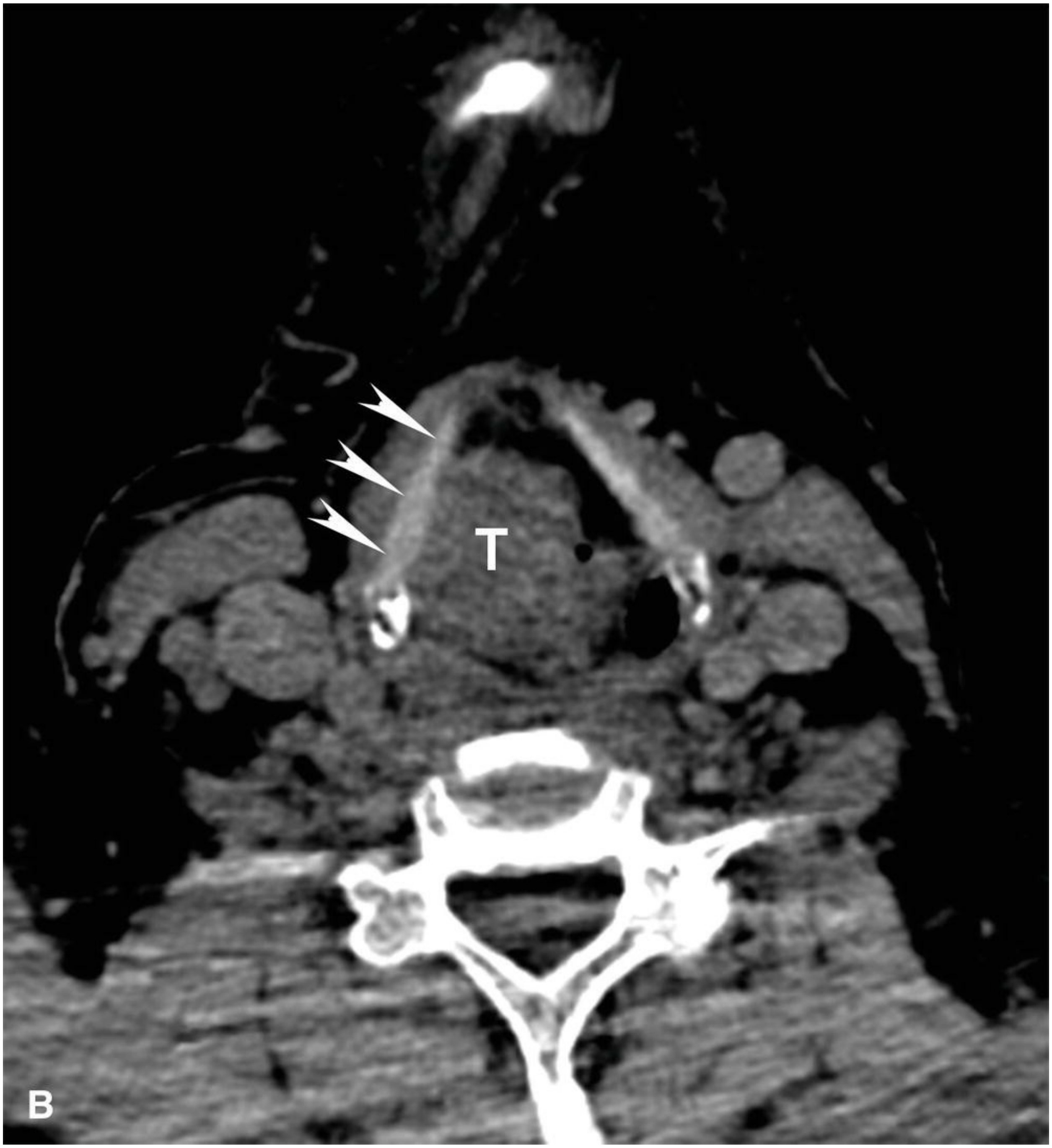


Figure 5.56. Dual-energy CT (DECT) virtual monochromatic images (VMI) for the evaluation of nonossified thyroid cartilage (NOTC). DECT images are shown from a patient with a right laryngeal cancer (T). **A:** On the 70 keV VMI, the NOTC (*arrowheads*) density is similar to tumor (T) and the interface with the abutting tumor is not very clearly seen. **B:** On high-energy 140 kev VMI, the density of iodine from tumor (T) is suppressed and a sharp interface seen between NOTC (*arrowheads*) and adjacent tumor (T).

Other Imaging Techniques for Evaluation of Head and Neck Cancer

Perfusion imaging, performed either with CT or MRI, has been investigated for evaluation of head and neck cancer. Although preliminary studies have suggested that perfusion imaging may be useful for predicting tumor response to treatment,[140,141] these studies require further validation and are currently not in routine use. With introduction of integrated PET-MRI units, this modality is also being explored for evaluation of head and neck cancer,[142,143] but so far, there are limited data available. Furthermore, with regard to the evaluation of the neck, PET-MRI will be prone to the same technical challenges that were described earlier for conventional MRI. In addition, obtaining whole-body coverage will be much more of a challenge with PET-MRI than CT. These represent interesting areas of future research.

CONCLUSIONS

Imaging is an integral part of proper staging, follow-up, and management of head and neck cancer. Optimal imaging of head and neck cancer patients requires familiarity with the different techniques, their strengths, and pitfalls and should be tailored to the primary site of interest based on results of the clinical assessment. Radiologic evaluation and interpretation of head and neck studies requires familiarity with the complex anatomy of the head and neck, patterns of spread of tumors at different sites, and the AJCC staging system. So armed, the radiologist can provide a clinically relevant evaluation and play a key role in determining optimal patient management as part of the multidisciplinary team.

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6 Anesthetic Management for Head and Neck Cancer Surgery

Angela Truong and Dam-Thuy Truong

On October 16, 1846, in a public demonstration in the Ether Dome of the Massachusetts General Hospital, William T.G. Morton administered inhaled ether to Edward G. Abbott for resection of a neck tumor by John C. Warren.[1] This milestone revolutionized the practice of medicine and surgery. It is noteworthy that at the birth of anesthesiology as a brand-new medical specialty, general anesthesia (GA) was provided for a surgical procedure in the neck. Over the centuries, while considerable scientific and technological advances have been achieved, the professional bond between head and neck surgery and anesthesiology has not only been preserved but also strengthened.

Anesthesia management for head and neck cancer surgery presents unique and often formidable challenges. The main predisposing factors to head and neck cancers are tobacco consumption and alcohol consumption.[2] Consequently, head and neck cancer patients often present with respiratory and cardiovascular comorbidities, which increase the complexities and challenges of the perioperative management. Furthermore, difficult airways are encountered in head and neck cancer surgery more commonly than in any other type of surgery. The invasion of the airway by tumors and the sequelae of previous surgical resections and/or radiotherapy or chemoradiotherapy may render mask ventilation and tracheal intubation difficult or even impossible after induction of GA. Finally, surgical and anesthesia teams must share their work space in the restricted area of the head and neck and the narrow confines of the airway. Surgeons require optimal exposure and complete access to the head and neck area or the airway itself. Anesthesiologists must achieve access and control of the airway to ensure adequate ventilation, oxygenation, and delivery of inhalation anesthesia.

Therefore, the demands for surgery and anesthesia may be in direct conflict. For example, in laser surgery for laryngeal tumors, the anesthesiologist may need to provide a high inspired concentration of oxygen to ensure adequate oxygenation of the patient, whereas the surgeon requires a low concentration to prevent fire. Constant communication between surgical and anesthetic team members can prevent intraoperative airway issues such as accidental extubation or disconnection of breathing circuits. This chapter highlights our personal daily work experience providing anesthesia for a high volume of head and neck cancer surgeries performed at the MD Anderson Cancer Center. Special emphasis will focus on the recent innovations in clinical anesthesia, which are of special interest to our surgical colleagues.

PREOPERATIVE EVALUATION OF ANESTHETIC RISK

The perioperative management of anesthesia for head and neck cancer surgery encompasses preoperative assessment and intraoperative and postoperative anesthetic management. The American Society of Anesthesiologists (ASA) Practice Advisory for Preanesthesia Evaluation considers the preoperative evaluation as the first and most fundamental component of anesthetic practice and requires that all patients scheduled for surgery under anesthesia receive a preoperative anesthetic evaluation.[3] This assessment also serves as a medicolegal document to be incorporated in the patient’s medical record. The objectives are to assess anesthetic-related risks and predict the likelihood of complications during the perioperative period for each patient undergoing a specific surgical procedure.[4] Furthermore, active interventions may be undertaken to modify these risk factors in the hope of reducing morbidity and mortality and improving outcomes. The preoperative evaluation allows the anesthesiologist to formulate the most appropriate perioperative plan for anesthesia care and to discuss with the patient about the risks and benefits in order to obtain an informed consent.

ASSESSMENT OF COEXISTING MEDICAL DISEASES

The preanesthesia evaluation includes pertinent medical history obtained from medical records and the patient interview, physical examination, and laboratory investigations. Preoperative tests should not be ordered routinely, but only when indicated for the purpose of guiding perioperative management, and may include hemogram, coagulation studies, serum chemistries, electrocardiogram, chest radiograph, and urine pregnancy test for female patients of childbearing age.[5] The information obtained allows anesthesia providers to categorize the overall physical health or sickness of patients before surgery according to the ASA physical status classification[6]:

1. A normal healthy patient
2. A patient with mild systemic disease
3. A patient with severe systemic disease
4. A patient with severe systemic disease that is a constant threat to life
5. A moribund patient who is not expected to survive without the operation
6. A declared brain-dead patient whose organs are being removed for donor purposes

For emergency cases, the letter E is added after the physical status class.

Even though the original intent of the ASA was to design a simple physical status stratification, the ASA classification has been used by hospitals, law firms, and health care organizations as a scale to predict perioperative risk.[7] In general, for low-risk procedures, ASA class 1 and 2 patients may proceed to surgery without further delay. In contrast, patients classified in ASA class 3 or higher may require appropriate specialty consultations to further investigate coexisting morbidities.

MEDICAL SPECIALTY CONSULTATIONS

For patients with multiple medical diseases, an internal medicine consultation is valuable to assess the severity of comorbid conditions, elicit further investigations, and institute measures to optimize the patient prior to surgery. Thus, the adjustment of antihypertensive medication dosages for better control of blood pressure and diabetes medications for improved blood glucose control may be achieved. Similarly, patients with congestive heart failure may be prescribed inotropes or diuretics. Patients with chronic

obstructive pulmonary disease may be treated with appropriate antibiotics, steroids, and/or bronchodilators. For cancers involving endocrine glands such as the thyroid and parathyroids, optimization of hormonal functional status by endocrinology consultation is an integral part of the surgical evaluation.

Considering that more than 50% of deaths after surgery are related to cardiac events, a cardiology consultation is warranted if the patient presents with severe cardiovascular diseases.[8] The American College of Cardiology/American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery base the need for further investigations on the presence of risk predictors for perioperative cardiac events, the patient's functional status, and the level of risk of the planned surgical procedure.[9]

Clinical predictors of increased risk for perioperative cardiac complications are classified into major, intermediate, and minor predictors. Major predictors include unstable angina, recent myocardial infarction, severe valvular heart disease, decompensated congestive heart failure, and significant arrhythmias. Intermediate predictors include stable angina, prior myocardial infarction by history or by electrocardiogram, compensated congestive heart failure, diabetes mellitus, and renal insufficiency. Minor predictors include advanced age, abnormal electrocardiogram, history of stroke, and uncontrolled hypertension.

The patient's functional capacity is the second major determinant of perioperative cardiovascular complications. Functional capacity or ability to work is measured in metabolic equivalents (METs). One MET equals the oxygen consumption of a 70-kg, 40-year-old man in a resting state. It is a physiologic measure expressing the energy cost of physical activities and is defined as the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific physical activity to a reference metabolic rate, set by convention as 3.5 mL O_2/kg/min.

The specific risk level inherent to the proposed surgical procedure must also be taken into consideration. High-risk surgeries include emergency, aortic, peripheral vascular, and radical head and neck cancer resection followed by complex free flap plastics procedures. Intermediate-risk surgeries include orthopedic, urologic, and uncomplicated abdominal and thoracic procedures. Many types of head and neck surgical procedures,

thyroidectomy, elective neck dissection, and parotidectomy also belong to this group. Low-risk surgeries include breast, cataract, and head and neck endoscopic procedures. As a rule, according to these guidelines, the planned surgery can proceed if it is an emergency surgery, if the surgical procedure is of low risk, or if the patient's functional status is equal to or greater than 4 METs without acute cardiopulmonary symptoms. In contrast, the presence of serious clinical predictors, low functional capacity, or high-risk surgery, either alone or in combination, indicates the need for further testing for left ventricular function or inducible coronary ischemia to determine if any intervention is indicated to optimize these risks before surgery.

PERIOPERATIVE MANAGEMENT OF PATIENTS WITH PACEMAKERS OR IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

Cardiac electronic devices such as pacemakers or implantable cardioverter defibrillators (ICDs) are encountered with increasing frequency in older patients presenting for head and neck surgery. The Heart Rhythm Society/American Society of Anesthesiologists suggests a preoperative check for these devices to determine the indication for implantation, adequate functioning of the device, and degree of pacemaker dependency.[10] Device malfunction or failure during surgery may result in serious injury and death. Prior to surgery, an ICD is programmed to a "monitor-only" mode to prevent inappropriate shock delivery from accidental sensing of electrical interference. To minimize the risk of intraoperative electromagnetic interference, the use of monopolar mode of operation of electrocautery should be avoided whenever possible.[11] When monopolar electrocautery is necessary, its use should be limited to intermittent short bursts. The electrocautery current return or grounding pad should be positioned so that the current pathway between the electrocautery electrode and return electrode is as far away from the device as possible. The application of a magnet over the pacemaker converts its function into a fixed rate mode. Unfortunately, the paced R wave may fall on the T wave of the patient's own beat and precipitate ventricular tachycardia or ventricular fibrillation due to R on T

phenomenon.[12] When the site of surgery is far from the chest, pads for an external pacing system should be applied. If the pacing pads are in the surgical field, a temporary transvenous pacing catheter should be inserted instead. Equipment for external pacing, defibrillation, and cardiopulmonary resuscitation should be immediately available. Close hemodynamic monitoring should be achieved with an arterial line and a cardiac output monitor. Hypoxia, acidosis, electrolyte abnormalities, and antiarrhythmic medications may cause pacemaker failure. Fentanyl, sufentanil, and remifentanil should be avoided because of risk of inducing severe bradycardia. Hydromorphone should be selected as the opioid of choice in these patients. At the conclusion of surgery, the device must be interrogated and reprogrammed to ensure proper functionality.

PREOPERATIVE OPTIMIZATION

In preparation for surgery, the patient's comorbidities should be medically optimized. Medications should be reevaluated and adjusted to achieve optimal blood pressure control in patients with hypertension and glycemic control in those with diabetes mellitus. Patients with severe chronic bronchitis and emphysema might require treatment with bronchodilators, steroids, and/or appropriate antibiotics. Congestive heart failure and unstable angina should be adequately treated. Cessation of smoking should be encouraged. Nutritional status should be improved. Preoperative psychological assessment and optimization is also crucial, yet often overlooked.[13] Many patients with head and neck cancer are clinically depressed at diagnosis. In addition to the anxiety related to being diagnosed with cancer, these patients must also deal with the disfiguring effects of craniofacial resection and loss of their natural voice in cases of laryngectomy.[14] Proper attention should be devoted to psychological preparation, particularly for children and young adults.

Preoperative Assessment of the Airway

Once the patient has been optimized and cleared for surgery, an assessment focused on specific intraoperative anesthetic considerations for anesthesia should be performed. The most important focus of the preanesthetic evaluation for head and neck cancer surgery is the assessment for a difficult

airway and formulation of a plan to secure the airway. Failure to secure the airway has been widely recognized as a leading cause of poor outcomes in the practice of anesthesia.[15] The single most important reason of failed airway management is the failure to properly assess the airway preoperatively and adequately anticipate difficulties in airway management.[16]

History obtained through review of medical charts and patient interview elicits information concerning previous general anesthetics and intubation difficulties. A history of difficult intubation should be taken into account even though the patient's airway may appear easy on routine examination. Furthermore, a past history of easy intubation does not guarantee that the patient remains easy to intubate because, in the interval, the tumor may have rapidly enlarged or postradiation trismus may have worsened. Special concern should be raised when the following warning signals about potential difficulties are encountered. By simply looking at the operating room schedule, the proposed surgical procedures may implicitly allude to a potentially difficult airway. Thus, emergency exploration of hematoma in the neck, drainage of a retropharyngeal abscess, and surgery for Ludwig angina often imply serious potential challenges with airway management. Even for elective cases, some of the planned procedures should raise alarm. For instance, total laryngectomy is scheduled usually because of extensive laryngeal involvement. Possible tracheostomy implies high risk of airway obstruction. Tracheal resection implies extensive involvement of the trachea by cancer that may impede passage of the tracheal tube. Physical examination of the patient also alerts anesthesia providers to the possibility of airway problems. Changes in the patient's voice may give valuable clues to the location of the tumor. A scratchy, raspy, hoarse voice often indicates a lesion of the vocal cords, whereas a muffled "hot potato" voice suggests a pharyngeal or supraglottic tumor. An anxious patient who is sitting up, leaning forward, drooling, and stridorous with use of accessory respiratory muscles is clearly in danger of impending complete airway obstruction. Tachycardia, tachypnea, and profuse sweating denote hypercapnia. Somnolence often heralds impending respiratory arrest. A foul-smelling odor should warn of a necrotic tumor. Grossly distorted anatomy with evidence of prior head and neck surgery and radiation therapy are all red flags. The presence of severe trismus, dysphagia, odynophagia, copious oral secretions, and bleeding from tumors indicate a high risk for airway difficulties.

The systematic airway assessment starts with the examination of the teeth to anticipate and prevent perioperative dental injury. Injury to the teeth is one of the most common anesthesia-related adverse outcomes.[17] It is also the most common cause for malpractice litigation against anesthesia providers.[18] Preexisting dental conditions that predispose to dental injury include severe gingivitis, capped teeth with veneers, permanent bridges, crowns, and implants. An isolated tooth adjacent to edentulous gums and preexisting loose tooth are susceptible to damage or dislodgement with even the slightest laryngoscope blade-tooth contact. Most dental damage occurs during intubation using rigid laryngoscopes. Dental injury may also occur during insertion and removal of an oral airway, intubating airway, tooth guard, or supraglottic device. The best method for prevention of dental injury is by performing fiberoptic nasal intubation.

Airway assessment for head and neck cancer surgery must take into consideration not only the features of the difficult airway common in previously untreated patients but also the potential difficulties in airway management caused by the effects of previous surgery and radiation therapy and the presence of tumor involving the airway. Many patients may have already undergone head and neck cancer surgeries. Common surgical procedures for neck and neck cancers such as thyroidectomy, parotidectomy, and neck dissection have relatively minor impact on subsequent management of the airway. In contrast, patients who have undergone extensive resection followed by complex free flap reconstruction, those with osteoradionecrosis of the mandible with exposed bone grafts and hardware, and patients with aggressive cancer recurrence often present with severely restricted mouth opening and bulky flaps in the oropharyngeal cavity. These changes distort the anatomy of the airway, rendering ventilation and intubation very challenging.

The majority of head and neck cancers are squamous cell carcinomas, which are relatively radiosensitive. Radiation therapy may cause severe burns followed by fibrosis of the local and regional tissues. Similarly, the effects of previous head and neck radiotherapy can render management of the airway extremely difficult. To compound this challenge, radiation effects are difficult to assess and often overlooked by anesthesia providers.[19] Acute radiation injury of the mucous membranes of the airway causes severe erythema, edema, and mucositis with thick white pseudomembranes.

Ulceration and necrosis may result in severe cases, with the affected area extremely vulnerable to mechanical trauma. The slightest mechanical injury during airway manipulation may cause bleeding and severe edema of the epiglottis and vocal cords, progressing rapidly to the inability to ventilate and to intubate. The fibrotic scar causes anatomic distortion and severe reduction in tissue flexibility and mobility: reduced mouth opening, limitation of neck motion, and laryngeal fibrosis.[20] Decreased secretion of saliva secondary to radiation burns of the salivary glands can result in xerostomia and fissures of the oral mucosa. Maintenance of oral hygiene is difficult, with resulting severe gingivitis and dental decay. Subacute and chronic effects involve the connective tissues and cause slow but progressive fibrosis. The affected skin appears retracted, discolored, atrophic, and cold. Involvement of the muscles of mastication and the temporomandibular joints can result in severely restricted mouth opening. The pharynx and supraglottic area may become fibrotic, fixed, and fused. The soft tissues of the airway lose elasticity, and the affected areas become indurated and retracted, resulting in severe limitation of neck extension. The submandibular area may become an irregular mass with a firm woody consistency to palpation. These affected structures are often immobile and unyielding to attempts at visualizing the larynx during laryngoscopy. For the same reasons, effective bag-mask ventilation and placement of an extraglottic device can be very challenging or even impossible.[21] Similarly, percutaneous cricothyrotomy or emergency tracheostomy to rescue the failed airway may encounter formidable difficulties due to the distorted anatomical landmarks and fibrotic tissue planes. An edentulous patient with Mallampati class I airway may appear deceptively easy to intubate. Overlooking the postradiation changes of the supraglottic area may rapidly lead to a “cannot intubate–cannot ventilate” crisis after induction of GA.

Tumors can cause difficulties in securing the airway because of their location, size and friability, and pathology. Location is the most important factor to consider. In general, tumors in the upper airway (nasal, oral, and pharyngeal lesions) are usually detected early and carry less risk of complete airway obstruction. In contrast, tumors involving the lower airway such as the supraglottic area, vocal cords, and trachea are more likely to cause greater challenges in airway management.[22] These tumors occupy a small volume space and may be more susceptible to causing complete obstruction.[23]

Fortunately, these lesions are usually detected early because of early symptoms. Epiglottic tumors are particularly insidious and deceptive. They can grow rapidly to reach a very large size and yet cause no respiratory symptoms.[24] Figure 6.1 depicts the laryngoscopic view after awake intubation showing the tracheal tube (A), epiglottis (B), and a large supraglottic Merkel cell carcinoma (C) covering the glottic opening. Carcinomas that are bulky, friable, and actively bleeding carry the risk of aspiration of tumor fragments and blood during traumatic intubation attempts.

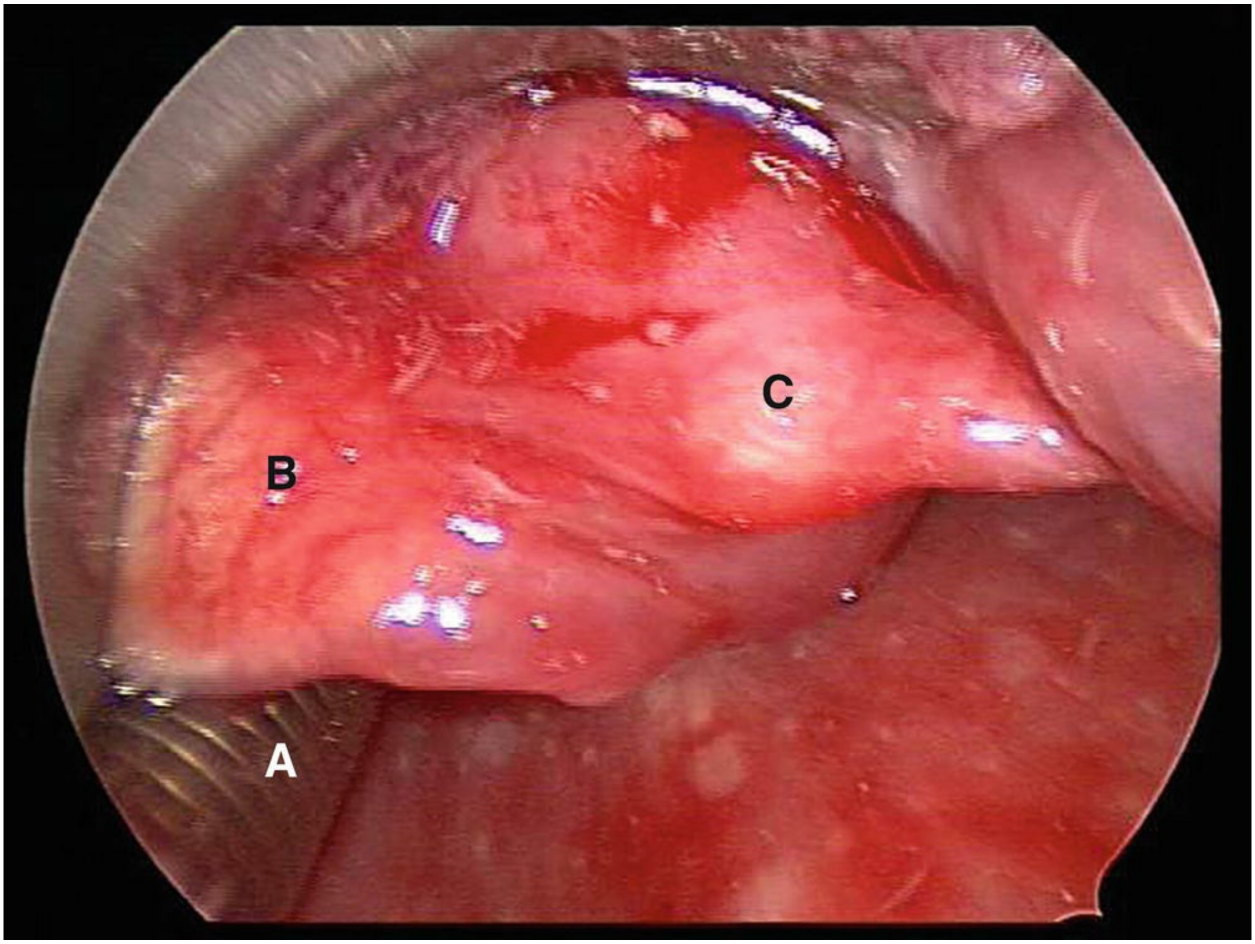


Figure 6.1. Laryngoscopic view of a supraglottic carcinoma.

Carcinomas deep inside the airway, which cannot be detected by visual inspection, require further investigation by diagnostic imaging and endoscopy. Chest radiographs of patients may show tracheal narrowing and/or deviation or widening of the superior mediastinum. CT scans of the

neck and chest are better able to assess the extent of the tumor and its effect on surrounding structures, especially tracheal compression, deviation, or invasion. Virtual bronchoscopy combines CT with computer-assisted image processing to produce intra- and extraluminal views of the airways as they would appear during actual bronchoscopy. Magnetic resonance imaging offers better assessment of cartilaginous and soft tissue anatomical structures in the evaluation of tumor extension and degree of airway obstruction.

Nasopharyngoscopy performed in the head and neck surgery clinic provides the anesthesiologist with valuable information about the location, size, and degree of airway obstruction caused by the tumor. For lesions in the glottic area, laryngoscopy videos show the tumor and the motion of the vocal cords during the respiratory cycle. If there is a long interval between these studies and the day of surgery, the attending anesthesiologist can perform nasopharyngoscopy under local anesthesia in the operating room before induction of GA to help decide on the best approach of securing the airway.[25] It is important to keep in mind, however, that the ability to visualize the glottic opening in an awake, spontaneously breathing patient does not guarantee that similar views can be obtained once the same patient is rendered unconscious, paralyzed, and apneic.

Airway Assessment Mnemonics

There is no substitute for a thorough systematic assessment of the airway. Nevertheless, in daily practice, aids such as airway mnemonics[26] are very useful as concise checklists specifically designed to quickly identify the features that may cause difficulties in various aspects of airway management. The most important mnemonics that help anticipate difficulty regarding ventilation, intubation, and risk of aspiration are MOANS, LEMON, and AEIOU. These should be used for every patient during routine preoperative airway assessment.

MOANS: To predict difficult bag-mask ventilation

M: Mask seal made difficult by the presence of facial hair

O: Obese with BMI > 26

A: Age older than 55 years

N: No teeth

S: Snores, sleep apnea

LEMON: To predict difficult rigid laryngoscopy and intubation

L: Looks difficult

E: Evaluate with 3-3-2: Able to insert 3 fingerbreadths inside the mouth; 3 fingerbreadths between the tip of the mentum and the junction of the mandible and the neck; 2 fingerbreadths between the base of the tongue and the larynx

M: Mallampati class[27]: Patient seated, mouth opening as large as possible, able to visualize the following structures:

Class I: Soft palate, tonsils, uvula, pillars

Class II: Soft palate, tonsils, uvula

Class III: Soft palate, uvula base

Class IV: Hard palate only

O: Obstruction of the upper airway

N: Neck mobility: Limited cervical spine mobility

AEIOU: To predict high risk of aspiration

A: Abscess, especially retropharyngeal abscess

E: Esophageal cancer, status post esophagectomy, esophageal reflux

I: Intubation difficulty necessitating prolonged mask ventilation and gastric insufflation

O: Obstruction: Gastric outlet and bowel obstruction

U: Unresponsive, lethargic, altered mental status

For head and neck cancer surgery, patients with exceptionally challenging airways may require airway control by surgical means. In these cases, the mnemonic SHORT may help to determine if cricothyrotomy or tracheostomy will be technically difficult.

SHORT: To predict difficult cricothyrotomy and tracheostomy

S: Surgical scar

H: Hematoma

O: Obese

R: Radiation

T: Tumor

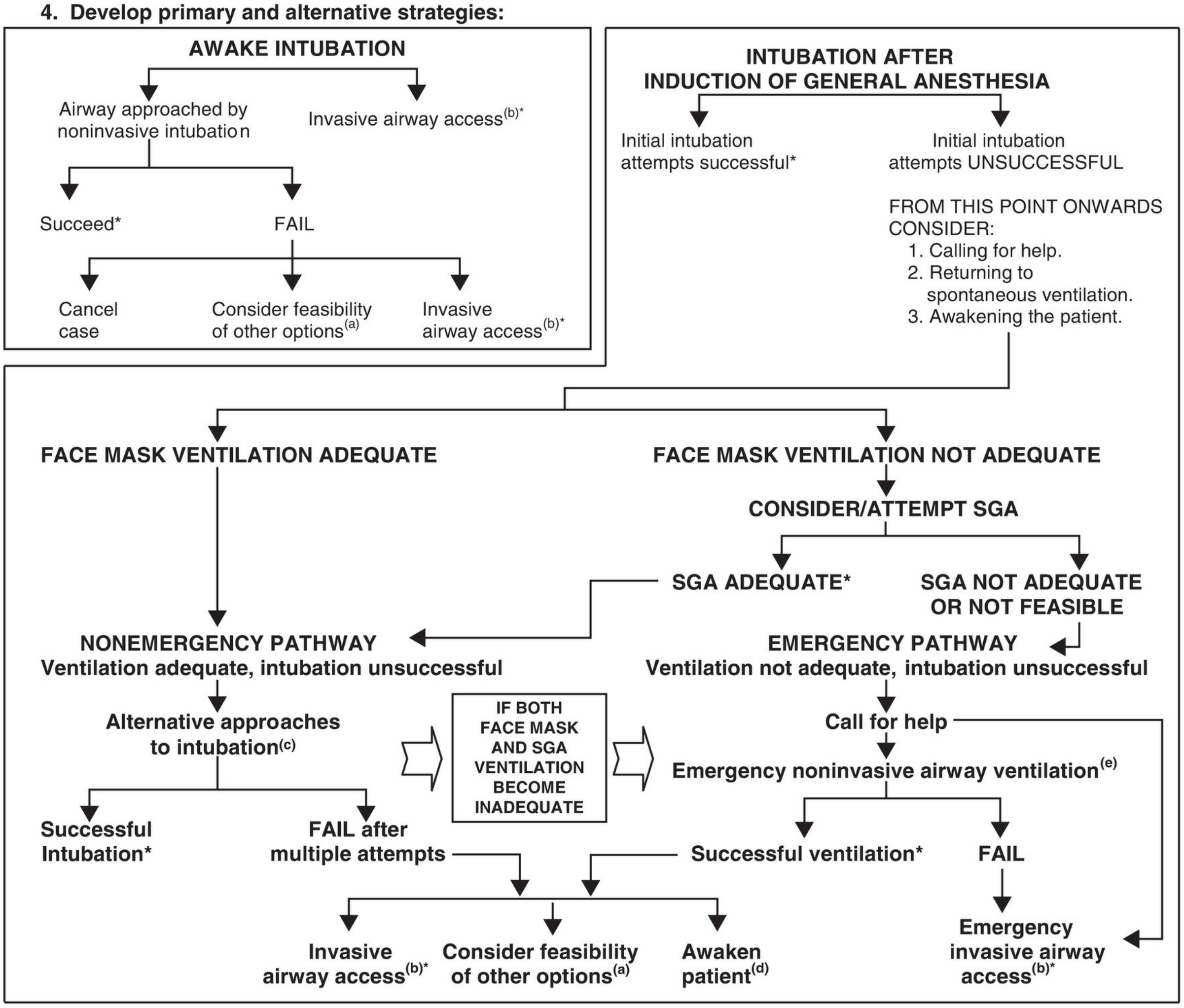
To reduce the need for multiple overlapping mnemonics, we propose a simplified yet comprehensive mnemonic, VIA, as will be discussed below.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS DIFFICULT AIRWAY ALGORITHM

Anesthesia providers are regarded as the experts in airway management. In the vast majority of cases, management of the airway is a routine part of our daily clinical practice, accomplished without problems. Unfortunately, failure to secure the airway occurs surprisingly often. Difficult mask ventilation has been reported to be as high as 5%[28] and failed ventilation in 0.1% of cases[29]. Furthermore, difficult intubation with a laryngoscope occurs in 1% to 4% and failed intubation in 0.05% to 0.35%. The incidence of “cannot intubate–cannot ventilate” situations that result in brain damage or death has been reported as 0.01 to 2.0 per 10,000 patients.[30] The potential for airway disasters continues to hang over our heads, like the sword of Damocles.

The ASA, recognizing the need to reduce the incidence of failed airways, published practice guidelines and an algorithm for management of the difficult airway in 1993, with a subsequent revision in 2003 and updated in 2013.[31–33] The purpose of this algorithm is to assist in the decision-making process to manage the difficult airway. This comprehensive algorithm presents an organized, systematic approach to various difficult airway scenarios and the management options available (Fig. 6.2). Unfortunately, the algorithm is not truly binary and for any given situation allows several management options, without clear specifications to what would be the best option under the circumstances. Its multiplicity of pathways drastically reduces its practical usefulness in real-life difficult airway scenarios, especially in a crisis situation. Adequate ventilation rather than successful intubation should be stressed as the end point. Patients die because of the inability to ventilate and not the inability to intubate. Often, adequate ventilation from use of an extraglottic device such as a laryngeal mask airway or waking the patient to resume spontaneous breathing can avert death by asphyxia, without the need for successful endotracheal intubation.

1. **Assess the likelihood and clinical impact of basic management problems:**
    - **Difficulty with patient cooperation or consent**
    - **Difficult mask ventilation**
    - **Difficult supraglottic airway placement**
    - **Difficult laryngoscopy**
    - **Difficult intubation**
    - **Difficult surgical airway access**
2. **Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.**
3. **Consider the relative merits and feasibility of basic management choices:**
    - **Awake intubation *vs.* intubation after induction of general anesthesia**
    - **Non-invasive technique *vs.* invasive techniques for the initial approach to intubation**
    - **Video-assisted laryngoscopy as an initial approach to intubation**
    - **Presvation *vs.* ablation of spontaneous ventilation**
4. **Develop primary and alternative strategies:**



***Confirm ventilation, tracheal intubation, or SGA placement with exhaled CO_2.**

a. Other options include (but are not limited to): surgery utilizing face mask or supraglottic airway (SGA) anesthesia (e.g., LMA, ILMA, laryngeal tube), local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.

b. Invasive airway access includes surgical or percutaneous airway, jet ventilation, and retrograde intubation.

c. Alternative difficult intubation approaches include (but are not limited to): video-assisted laryngoscopy, alternative laryngoscope blades, SGA (e.g., LMA or ILMA) as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery.

e. Emergency non-invasive airway ventilation consists of a SGA.

Figure 6.2. ASA Difficult Airway Algorithm. (From Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2013;118:251–270, with permission.)

While the ASA algorithm may be viewed as cumbersome and difficult to apply to daily clinical practice, this decision-making tree provides evidence-based guidelines to make appropriate airway management decisions. Most airway disasters occur after induction of GA and administration of muscle relaxants, which result in loss of consciousness, apnea, and airway obstruction. Problems arise from the inability to intubate and inability to ventilate. In retrospect, these catastrophes could have been prevented by performing an awake fiberoptic intubation (FOI) to secure the airway before inducing GA. Choosing to perform an awake FOI has very clear advantages. Spontaneous ventilation is maintained at all times by a cooperative patient who is able to protect his or her airway against aspiration. During administration of topical anesthesia to the airway and awake FOI, an awake patient is better able to cooperate, generate deep inspiratory efforts, protrude the tongue, and perform other maneuvers that will help the anesthesiologist successfully visualize the glottis. With effective topical airway anesthesia and judicious administration of sedation, excellent success rates of awake intubation can be achieved.

The disadvantages of awake FOI include the time required to properly topicalize the airway, the potential risk of local anesthetic toxicity if excessive amounts of local anesthetic are used, and in uncooperative patients, this procedure may be very difficult to perform. Finally, the real possibility of recall of the procedure may occur in cases when not enough amnestic medications are given. For these reasons, awake intubation should not be done routinely in most cases. It should be chosen only for appropriate situations when it is deemed necessary. The main reason why this option is not selected in cases of unanticipated difficult airway is the lack of clear guidelines or criteria for awake intubation. The ASA Difficult Airway Algorithm does not address this important issue.

THE "VIA" SCORING SYSTEM FOR

DIFFICULT AIRWAY

In an effort to address this need, we have designed a novel approach to assess the difficult airway that takes into consideration the impact of head and neck cancers on each of the three determinants that underlie causes of morbidity and mortality during airway management: ability to ventilate (V), ability to intubate (I), and risk of gastric aspiration (A). Each of these determinants can potentially cause detrimental effects on another determinant. For example, a case of difficult intubation with multiple attempts at laryngoscopy may lead to difficult ventilation from ensuing airway edema. In turn, prolonged ineffective mask ventilation results in gastric insufflation, leading to aspiration (Fig. 6.3). By devising a scoring system that takes into account the severity of each of these factors, we can stratify the risks and make a logical decision on which technique of airway management is most appropriate for each individual case. The VIA scoring system helps anesthesiologists to make a systematic and rational decision regarding airway management by focusing on all three determinants of airway management. It serves as a concise, quick-to-perform “time-out” before proceeding with induction of GA. In contrast to other airway assessment approaches, which evaluate airway difficulty only in awake patients, the new emphasis of this scoring system focuses on anticipating these risks of airway problems after loss of consciousness is induced by general anesthesia. Depending on the severity of risk of difficulty to ventilate, difficulty to intubate, and risk of aspiration, a numerical grade is assigned to each determinant.

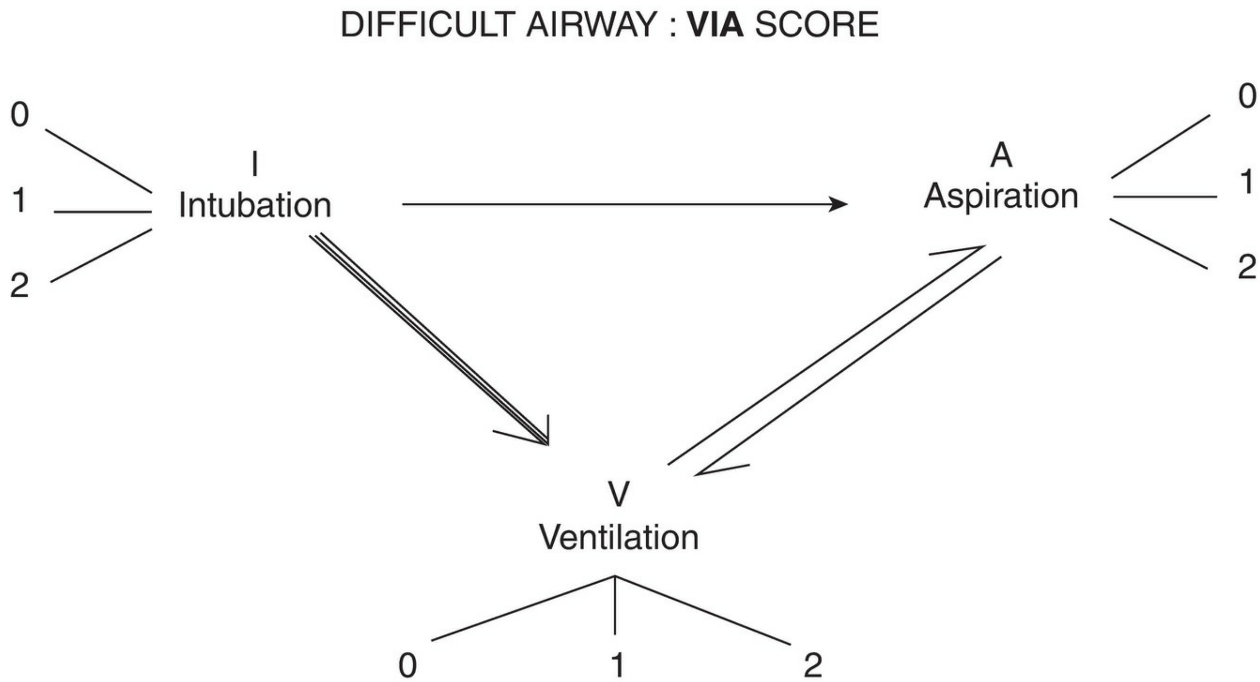


Figure 6.3. VIA score.

Each determinant V, I, and A is graded separately and assigned a numerical score according to severity: 0 = no risk; 1 = potential risk of difficulty, believed to be readily overcome by routine maneuvers; 2 = definite risk of difficulty, which may not be overcome by routine maneuvers.

For ventilation:

0 = bag-mask ventilation effective; 1 = extraglottic device needed to ensure adequate ventilation; 2 = impossible to ventilate after induction of GA

For intubation:

0 = successful with rigid laryngoscopes; 1 = flexible fiberoptic bronchoscope needed; 2 = impossible to intubate after induction of GA

For aspiration:

0 = no special risk; 1 = risk of aspiration can be overcome by rapid sequence induction and cricoid pressure; 2 = high risk of aspiration

After each factor is graded, their summation results in a total score from 0 to 6. From this total VIA score, a more rational approach to managing the difficult airway is proposed:

Total Score

0–1 Low risk for adverse respiratory events; may proceed with conventional induction of GA and conventional airway management

2–3 Moderate risk for adverse respiratory events; proceed with awake FOI

4–6 High risk of adverse respiratory events; proceed with awake tracheostomy

In order to prevent unilateral decision-making and misunderstanding, the preoperative communication and collaboration between anesthesiologist and surgeon to elaborate a joint perioperative plan will contribute to the mutual understanding of each other's needs. The anesthesiologist should be made aware of all the successive steps and demands of the surgical procedure. Likewise, the surgeon should be informed of the patient's significant medical conditions and the need for special intraoperative monitoring or treatment. In unusually complex or challenging cases, senior colleagues with greater experience and expertise should be consulted to discuss the anesthetic plan and request technical assistance in securing the airway.

Intraoperative Airway Management: Ventilation

Management of the airway should focus first and foremost on ensuring adequate ventilation and oxygenation.[34] It is surprisingly difficult to predict difficult or impossible mask ventilation.[35] If bag-mask ventilation is not adequate with use of an oral or nasopharyngeal airway, insertion of a supraglottic device such as the laryngeal mask airway or LMA (Teleflex Medical, Research Triangle Park, NC) can provide rescue ventilation. In contrast to a face mask held over the face for conventional bag-mask ventilation, a supraglottic device bypasses tissues of the oropharyngeal cavity and establishes a direct conduit to the glottic opening, enabling more effective ventilation. Furthermore, the LMA may serve to provide GA without an endotracheal tube (ETT) and functions as an adjunct to facilitate orotracheal intubation. Compared to the ETT, the LMA is easier to place correctly, causes minimal hemodynamic response upon insertion, is better tolerated, and is associated with reduced coughing and bucking on emergence. The original LMA Classic is too rigid and has too a high profile to allow adequate field avoidance in head and neck surgery. In contrast, the LMA Flexible has a flexible wire-reinforced airway tube that allows it to be positioned away from the surgical field without kinking and without loss of cuff seal. Consequently, it is most appropriate for short head and neck

procedures. Finally, thanks to a tighter seal of the cull around the glottis, it has been used safely for adenotonsillectomy, dentoalveolar, and nasal surgery. The other popular LMA models are the LMA Unique designed for single use, the intubating LMA Fastrach, the LMA Proseal equipped with a separate gastric drainage channel to help prevent aspiration, and the LMA Supreme combining the advantages of the designs of the Fastrach and the Proseal. In contrast to the LMA, the I-Gel (Intersurgical, Wokingham, UK) is a new supraglottic device with a noninflatable mask made of gel-like thermoplastic elastomer and a gastric drainage channel similar to the Proseal.

Intraoperative Airway Management: Intubation

The major intraoperative problems that may arise concerning the ETT involve dislodgement or kinking. These problems may occur during any type of surgery, but occur much more frequently in head and neck surgery because the ETT is very close to the surgical field. For short cases, standard clear polyvinyl chloride (PVC) tracheal tubes are usually adequate. For most head and neck cases, these high-profile tubes are too rigid to be effectively directed away from the surgical field without kinking. To minimize these risks, the RAE (Ring, Adair, Elwyn) tube (Mallinckrodt, Pleasanton, CA) was specifically designed with preformed bends shaped to closely follow the natural contour of the patient's facial features so it can assume a low profile and minimize intrusion into the surgical field. Oral RAE tubes are positioned and taped down on the chin or at the corner of the mouth away from the surgical field. They are most useful for nasal, ophthalmic, and craniofacial surgeries. In contrast, nasal RAE tubes are positioned upward, directed toward the forehead for oral and maxillofacial procedures. Both oral and nasal RAE tubes can be temporarily straightened and armed onto a flexible bronchoscope for FOI. This preformed design presents an important problem in certain patients, depending on their particular individual airway anatomy. Once inserted into the trachea, the preformed tube tip may be too long, resulting in endobronchial intubation, or too short, resulting in accidental extubation. Surgical manipulation such as head extension or flexion after taping the tube may also cause tube malposition. For some patients with an unusually long or short trachea, there may not be a commercially available preformed RAE tube that would fit their airway anatomy. Furthermore, because of its tight bend, passage of a suction catheter through the tube is often difficult or even impossible. Finally, like any PVC tube, these tubes

may become softened by body heat during long cases and can become easily compressed and collapsed.

Complete airway control throughout the procedure is absolutely necessary in head and neck surgery. In our practice, we use almost exclusively the Parker Flex-Tip (Anandic Medical Systems AG, Diessenhofen, Switzerland) tracheal tube. This reinforced tube is designed with a spiral of wire embedded into the wall of the tube to confer strength and flexibility without kinking. It can be easily bent and taped down away from the field to improve surgical access. In addition, its curved, tapered ski-tip–shaped and centered distal tip was designed to minimize the tube from impaction with the anterior tracheal rings. This symmetric tip also prevents the tube from being hung up by laryngeal structures during passage through the glottic opening. This feature is especially useful for FOI because, even though insertion of the bronchoscope into the trachea is performed under direct vision, the actual insertion of the tube into the trachea is a blind maneuver and these tubes significantly decrease the incidence of tube hang-ups.

Used for recurrent laryngeal nerve monitoring to minimize the risk of vocal cord palsy, the NIM EMG ETT (Medtronic, Minneapolis, MN) is a flexible silicone tube fitted with four stainless steel wire electrodes embedded in the wall of the tube.[36] The short segment of these electrodes exposed just above the cuff must be in contact with the vocal cords to enable proper monitoring of electromyographic activity of the intrinsic laryngeal musculature. Avoiding the use of lidocaine gel or cream to lubricate the tube or lidocaine spray on the vocal cords is advised. Similarly, muscle relaxants are not used to preserve optimal laryngeal muscle function.

To minimize the risk of fire and tracheal tube being burned by the laser beams, some tubes specifically designed for laser surgery use metallic covering to protect the tubes made of rubber or polyvinylchloride tubes. The Xomed Laser-Shield II (Medtronic, Minneapolis, MN) tube incorporates an aluminum wrap around the silicone based tube. Similarly, the Laser-Trach Sheridan red rubber tube (Teleflex Medical, Research Triangle Park, NC) is covered with copper. These tubes are still vulnerable to being punctured by the laser beam. In contrast, tubes that are made entirely of flexible stainless steel such as the Laser-Flex (Mallinckrodt, Glen Falls, NY) offer much more secure protection against laser-induced fire. Because the shaft of a Laser-Flex

tube is unmarked, before intubation, it should be marked by comparing it to a similar sized marked tube to identify the length of intubation needed to achieve optimal tube positioning and prevent endobronchial intubation. Most laser tubes come with two PVC cuffs, which should be filled with water. Even if one cuff gets punctured by the laser beam, the cuff seal is maintained by the second cuff, and the leaking water will help extinguish fire in the vicinity. Methylene blue may be added to the cuff to facilitate detection of cuff rupture.

For patients with easy airways, rigid laryngoscopes using Macintosh curved or Miller straight blades are usually used for tracheal intubation. These “direct” laryngoscopes rely on the ability to expose and achieve a straight direct line of sight from the operator’s eyes to the larynx. Unfortunately, the glottis opening is difficult to visualize in 10.7% of patients with the head in simple extension position and 11.4% in the sniffing position.[37] Repeated unsuccessful attempts may lead to airway trauma and complete airway obstruction. This limitation led to the development of indirect rigid fiberoptic laryngoscopes, which allow easier visualization of the larynx through fiberoptic bundles. The image of the glottis is conveyed to an eyepiece or to a video display. The images on the video screen are invaluable for teaching and research. The AirTraq optical laryngoscope (Prodol Meditec S.A., Vizcaya, Spain) is a single-use indirect fiberoptic intubating device that allows visualization of the glottic opening without the need to align the oral with the pharyngeal and laryngeal axes. Consequently, successful tracheal intubation can be achieved with minimal head manipulation. The insertion of the blade requires a minimal mouth opening of 18 mm for the regular size and 16 mm for the small AirTraq. This device is most useful in patient with limited neck mobility, restricted mouth opening, and an anterior placed larynx. The cost of this fully disposable unit is equivalent to the cost of processing a standard laryngoscope blade and handle. The C-MAC video laryngoscope (Karl Storz Endoscope, Stafford, TX) is available in both Macintosh and Miller blade shapes. The image on the distal lens is acquired using a complementary metal-oxide semiconductor chip. A diffuse light-emitting diode with a high light output ensures adequate illumination of the application area. The GlideScope (Saturn Biochemical Systems, Burnaby, BC) incorporates a high-resolution digital camera with a video cable to a liquid crystal display (LCD) monitor. This laryngoscope consists of a medical-grade plastic modified Macintosh-type blade with its distal half

angled upward 60 degrees to improve the view of the glottis by reducing the requirement for anterior displacement of the tongue. The blade also incorporates a miniature video chip and light-emitting diodes providing adjustable illumination and contrast. The video image is transmitted by a cable to a dedicated LCD video display.

FLEXIBLE FIBEROPTIC INTUBATION TECHNIQUES

Flexible FOI is generally considered the gold standard for management of the difficult airway, especially when the degree of difficulty is compounded by invasion of the airway by tumors.[38] Life-threatening “cannot intubate–cannot ventilate” scenarios usually occur from repeated unsuccessful traumatic intubation attempts using rigid laryngoscopes. In contrast, flexible FOI is less traumatic and ventilation often preserved even after repeated attempts. There is much less risk of trauma to lips, teeth, tongue, and lesions of the oropharyngeal cavity compared to rigid techniques. Similarly, intubation injury to oropharyngeal free flaps or other reconstructed areas is minimized. This procedure causes less sympathetic stimulation than rigid laryngoscopy, an effect especially beneficial in patients with ischemic heart disease. The small diameter (3.5 to 6 mm) of the bronchoscope’s shaft allows it to be inserted in small openings such as the nostrils, the mouth in cases of trismus, and even in patients with jaws completely clenched using the retromolar space. Its flexibility permits the bronchoscopist to follow the anatomy of the airway in cases distorted by tumor, radiation therapy, or previous surgery. Finally, the use of the flexible fiberoptic bronchoscope before actual intubation permits a complete airway assessment from above and below the glottic opening. Not only is the larynx visualized but also subglottic lesions such tracheal strictures, tracheomalacia, and compression by goiter or an anterior mediastinal tumor may be detected.

Awake Intubation for Anticipated Difficult Airway

Awake FOI is the gold standard for the patient with an anticipated difficult airway. Unfortunately, this procedure is often an unpleasant and frightening ordeal for the patient. Conscious sedation is often needed to supplement topical anesthesia of the airway. The goal is to provide comfort for the patient

while preserving patient safety. The mucosa of the nose, pharynx, and larynx is exquisitely sensitive. Topical application of local anesthetics and/or performance of nerve blocks is needed to minimize the patient's discomfort and obtund gag and cough reflexes. Adequate anesthesia of the airway mucosa with local anesthetics constitutes the most important requirement for successful awake intubation, making in many cases the difference between success and failure.[39] Drying the airway serves two important purposes in awake intubation. Copious secretions in the airway may make adequate topicalization impossible, and secretions also render flexible FOI difficult. Glycopyrrolate 0.2 mg IV given before topicalization is most commonly used because of its antisialagogue effect. Compared to other anticholinergic agents such as scopolamine or atropine, its rapid onset, strong drying properties, and lack of sedation make it an ideal choice. Glycopyrrolate also enhances absorption of topical lidocaine and prolongs its duration of action.[40]

Topical Anesthesia of the Airway for Awake Intubation

A solution of 4% lidocaine is the local anesthetic most commonly used[41] because of its rapid onset (2 to 5 minutes), duration of action (30 to 60 minutes), and excellent safety record and effectiveness.[42] The effect of topical 2% lidocaine administered with an atomizer[43] using the "spray-as-you-go" technique through the bronchoscope[44] has been reported to be as satisfactory as 4% lidocaine. In contrast, topical anesthesia with atomized 1% lidocaine has been proven to be insufficient for airway manipulation.[45] The maximum recommended dose for topicalization is 6 mg/kg.[46] The most effective method of application is by atomization. The location where atomized droplets are deposited and absorbed depends on their size. Droplets diameter of 2 μm reach the farthest to the alveoli, 8 μm to the bronchioles, and 15 μm to the bronchi. The optimal droplet size that provides good topicalization of the vocal cords and upper trachea is 40 to 60 μm.[47] This is best achieved with a nebulizer such as the EZ-Spray (Alcove Medical, Houston, TX) with an oxygen flow rate set at 6 to 8 L/min.[48] Following the application of a vasoconstrictor to the naris, a nasopharyngeal trumpet coated with lidocaine jelly is inserted to serve as a conduit to spray local anesthetic deeper within the pharynx using the EZ-Spray. Finally, the MADgic Laryngo-Tracheal Mucosal Atomisation Device (Wolfe Tory Medical, Salt Lake City, UT) inserted deep into the trumpet and positioned just above the

vocal cords to spray 3 mL of atomized lidocaine will propel local anesthetic directly toward the glottic opening. For oral intubation, supplemental anesthesia may be achieved with 4% lidocaine gargle for oropharyngeal anesthesia. In cases of supraglottic tumors and distorted airways that may impede local anesthetic from reaching the larynx, topicalization can be performed by injecting lidocaine through the suction channel of the bronchoscope as it is advanced toward the glottis. To avoid the loss of local anesthetic along the lumen of the bronchoscope, this "spray-as-you-go" technique can be accomplished by threading an epidural catheter through the bronchoscope suction channel and used for spraying. When rapid airway topicalization is required, Cetacaine, a topical anesthetic mixture of 14% benzocaine and 2% tetracaine, is a popular option. Supplied with a convenient Jetco cannula, its onset of action is within 30 seconds, faster than lidocaine. Side effects include hypersensitivity reactions and risk of methemoglobinemia. Cocaine is a unique local anesthetic that produces vasoconstriction of the nasal mucosa. Severe coronary artery vasoconstriction and hypertension make this controlled substance much less routinely used.

Regional anesthesia of the upper airway by blockade of the branches of the trigeminal, glossopharyngeal, superior laryngeal, and recurrent laryngeal nerves provides effective anesthesia for awake intubation. In the presence of tumors in the airway along the path of the needle, regional nerve blocks are generally contraindicated. In very extensive supraglottic tumors, the bulky tumors impede topical anesthesia from reaching the vocal cords. Intubation may be unsuccessful due to patient coughing when the bronchoscope comes into contact with the supraglottic area. To overcome this problem, we described the retrograde translaryngeal injection of lidocaine. Directing the angiocatheter cephalad toward the vocal cords and deliberately timing the injection of lidocaine with the patient's forceful exhalation boosts the entrainment of local anesthetic upward to the supraglottic area (Fig. 6.4). These modifications allow upward flow of lidocaine across the vocal cords, reminiscent of a geyser's eruption.[49]

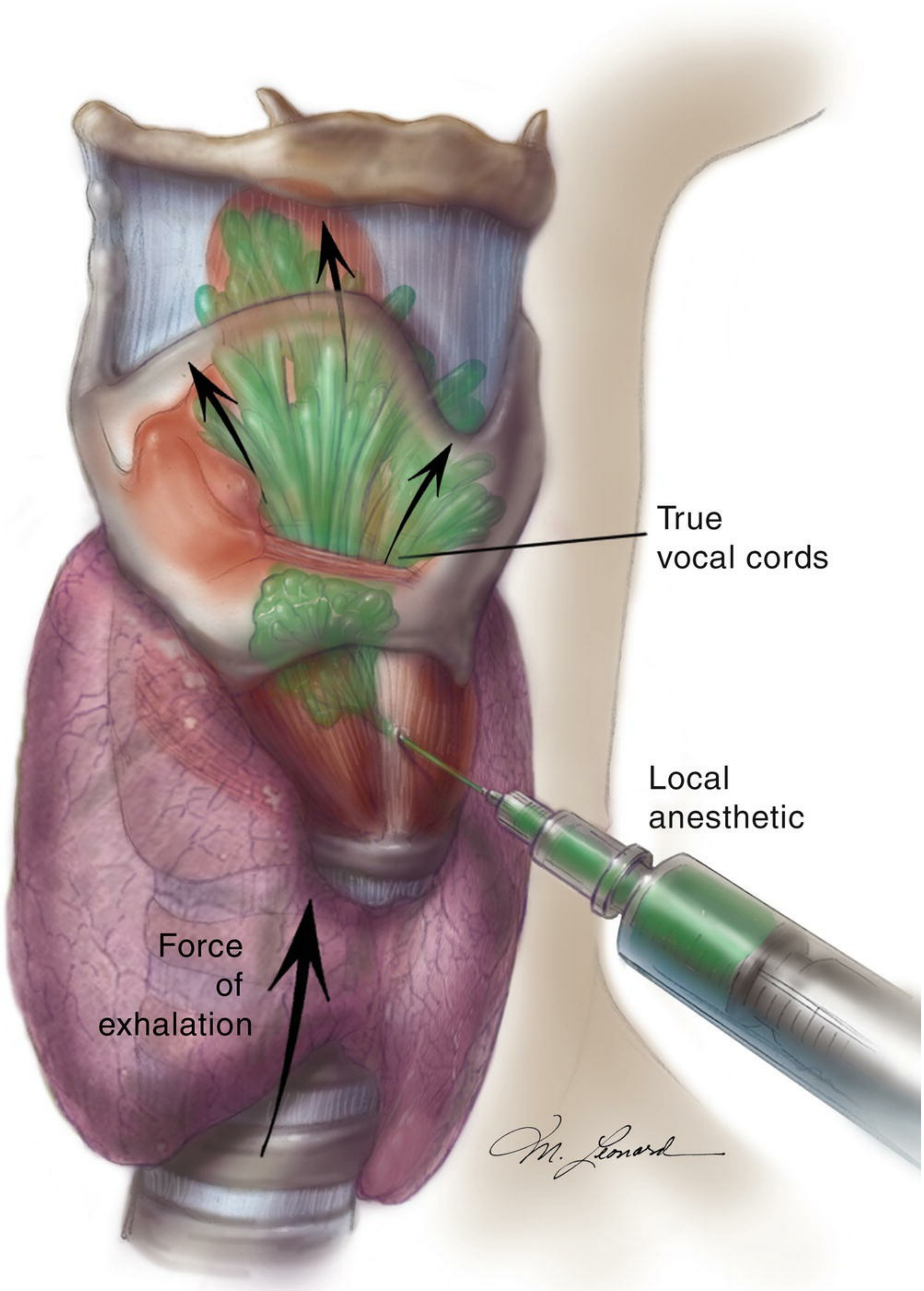

True
vocal cords
Local
anesthetic
Force
of
exhalation
M. Leonard

Figure 6.4. Retrograde translaryngeal injection. (Adapted from Truong A, Truong DT. Impossible awake intubation turned successful: topical anesthesia of the supraglottic area by retrograde translaryngeal injection of lidocaine timed with forceful exhalation. *Anesthesiology News: Guide to Airway Management.* 2012;66–67, with permission.)

INTRAVENOUS AGENTS FOR CONSCIOUS SEDATION

Even with adequate topical anesthesia of the airway, awake intubation may be a distressing and frightening ordeal for patients. In most cases, conscious sedation must be carefully tailored to the needs of the patient. Intravenous drugs should not be used to compensate for inadequate topical anesthesia of the airway mucosa. Sedation should be used very sparingly in cases of high risk of airway obstruction to ensure adequate spontaneous breathing and patient cooperation. In very anxious patients, midazolam 1 to 2 mg IV may be titrated to effect. Besides relieving anxiety, it also provides amnesia and may raise the threshold for convulsions in the event of local anesthetic toxicity. Different pharmacologic agents including hypnotics, narcotic analgesics, and alpha-2 adrenoceptor agonists have been used either alone or in combination for conscious sedation during awake intubation.[50] Surprisingly, propofol, the most commonly used drug for routine GA and monitored anesthetic care, is not well suited for awake intubation because of the high incidence of frequent coughing, abrupt loss of consciousness, apnea, and airway obstruction. Compared to propofol, a target-controlled infusion of remifentanil provides safer and better intubating conditions with less coughing and less airway obstruction.[51] Compared to remifentanil, dexmedetomidine provides comparable intubating conditions but fewer tachycardia episodes, less recall, and better patient satisfaction.[52] If there is no danger of impending airway obstruction, we routinely use dexmedetomidine as a continuous infusion from 0.1 to 0.7 μg/kg/min. This alpha-2 adrenoceptor agonist provides adequate sedation for the patient able to maintain airway patency and remain easily arousable in order to cooperate during the procedure.

RETROMOLAR FIBEROPTIC INTUBATION IN SEVERE TRISMUS

Tracheal intubation ensures control and protection of the airway for surgical procedures requiring GA. The approach, oral or nasal, depends on surgical requirements and the patient's ability to open the mouth fully. Orotracheal intubation is usually the preferred option. This procedure may be difficult or even impossible if mouth opening is restricted enough to preclude the insertion of a laryngoscope or an ETT between the teeth.

Originally defined as reduced opening of the jaws caused by spasm of the muscles of mastication, trismus now refers to limited mouth opening from any cause. Patients with this condition are encountered with increasing frequency in clinical practice. The prevalence of trismus has been reported to be from 5% to 38% after surgery and radiotherapy for head and neck malignancies.[53] In these cases, nasal intubation constitutes the customary alternative. Unfortunately, in some patients, there exist concomitant contraindications to nasal intubation. These include surgical procedures involving the nose, nasal pathology, history of basal skull fractures, and coagulopathy. Consequently, in patients with significant trismus and contraindications to nasal intubation, access to the airway through a surgical tracheostomy is an option of last resort. To avoid the need for tracheostomy, an invasive procedure with many potential serious complications, we described a novel technique using the retromolar space (Fig. 6.5) as an entry to perform flexible fiberoptic orotracheal intubation. We have reported three cases of retromolar placement of tracheal tubes in patients with severe trismus and difficult airways. The first report described retromolar fiberoptic orotracheal intubation (Fig. 6.6) in a patient with severe trismus undergoing nasal surgery.[54] This technique was also used successfully in a pediatric patient with a difficult airway and bilateral nasal stenoses.[55] Finally, we used the retromolar space to insert a double-lumen tube for lung isolation in a patient with a difficult airway.[56] We have also used this technique in patients with poor dentition to prevent dental injury. The retromolar approach offers several significant advantages. It can be performed in extreme cases of trismus, even in complete mandibular occlusion. By bypassing the oral cavity, the path to the glottic opening is shorter as compared to the midline oral approach. Consequently, intubation trauma to the lips, teeth, tongue, and

intraoral lesions can be avoided. Furthermore, the availability of the right and left retromolar space offers two locations for intubation to choose from. Even in the presence of tumor involvement of one retromolar space, the contralateral space may be used for intubation. The decision to perform retromolar intubation in the awake patient versus after induction of anesthesia should be made on an individual case-by-case basis. If there is any concern about difficult ventilation after induction of GA, awake FOI should be selected for patient safety. Finally, based on our experience teaching residents in training, this technique is surprisingly easy to learn. The skills required to perform flexible fiberoptic retromolar intubation are essentially the same needed for conventional oral and nasal FOI. By obviating the need for nasal intubation or tracheostomy, the retromolar approach should be considered as a valuable option for flexible bronchoscopic intubation in patients with severe trismus.

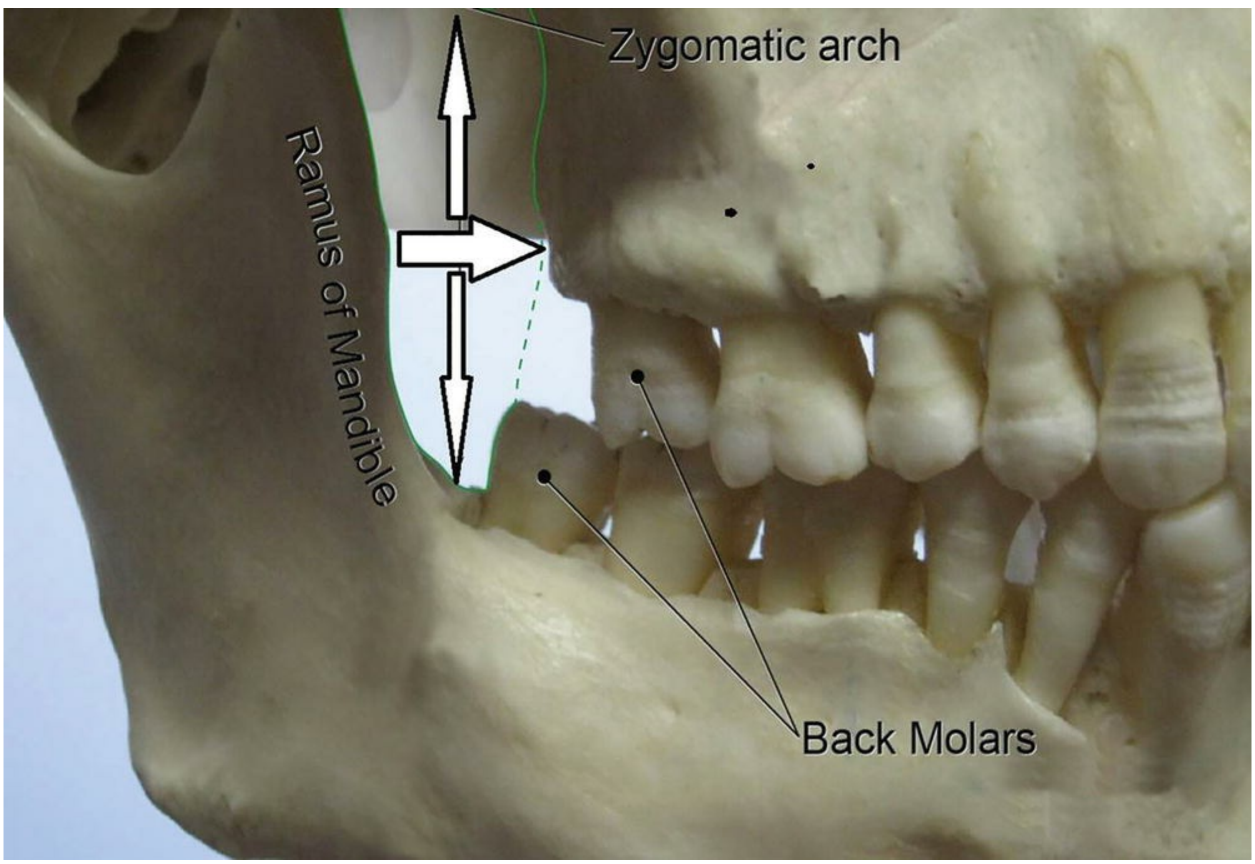


Figure 6.5. Retromolar space. (From Truong A, Truong DT. Retromolar fibreoptic orotracheal intubation in a patient with severe trismus undergoing nasal surgery. *Can J Anaesth.* 2011;58:460–463, with permission.)

Figure 6.6. Retromolar intubation. (From Truong A, Truong DT. Retromolar fibreoptic orotracheal intubation in a patient with severe trismus undergoing nasal surgery. *Can J Anaesth.* 2011;58:460–463, with permission.)

In case of unfamiliarity with the retromolar approach, we modified an Ovassapian Fiberoptic Intubating Airway (Bay Medical, Brisbane, CA) to increase mouth opening in patients with trismus enough to accommodate the passage of an ETT.[57] The minimum mouth opening that allows passage of the 6.0 mm ETT with an outside diameter of 8.2 mm is about 9 to 10 mm. In patients with maximal mouth opening of 7 to 8 mm, an Ovassapian airway can be modified by cutting out the proximal ring of the intubating channel and used as a slanted wedge (Fig. 6.7). Inserted between the teeth and gently advanced in the oral cavity (Fig. 6.8), mouth opening may be increased by 2 to 3 mm to reach 10 mm, wide enough to accommodate successful oral intubation between the teeth.

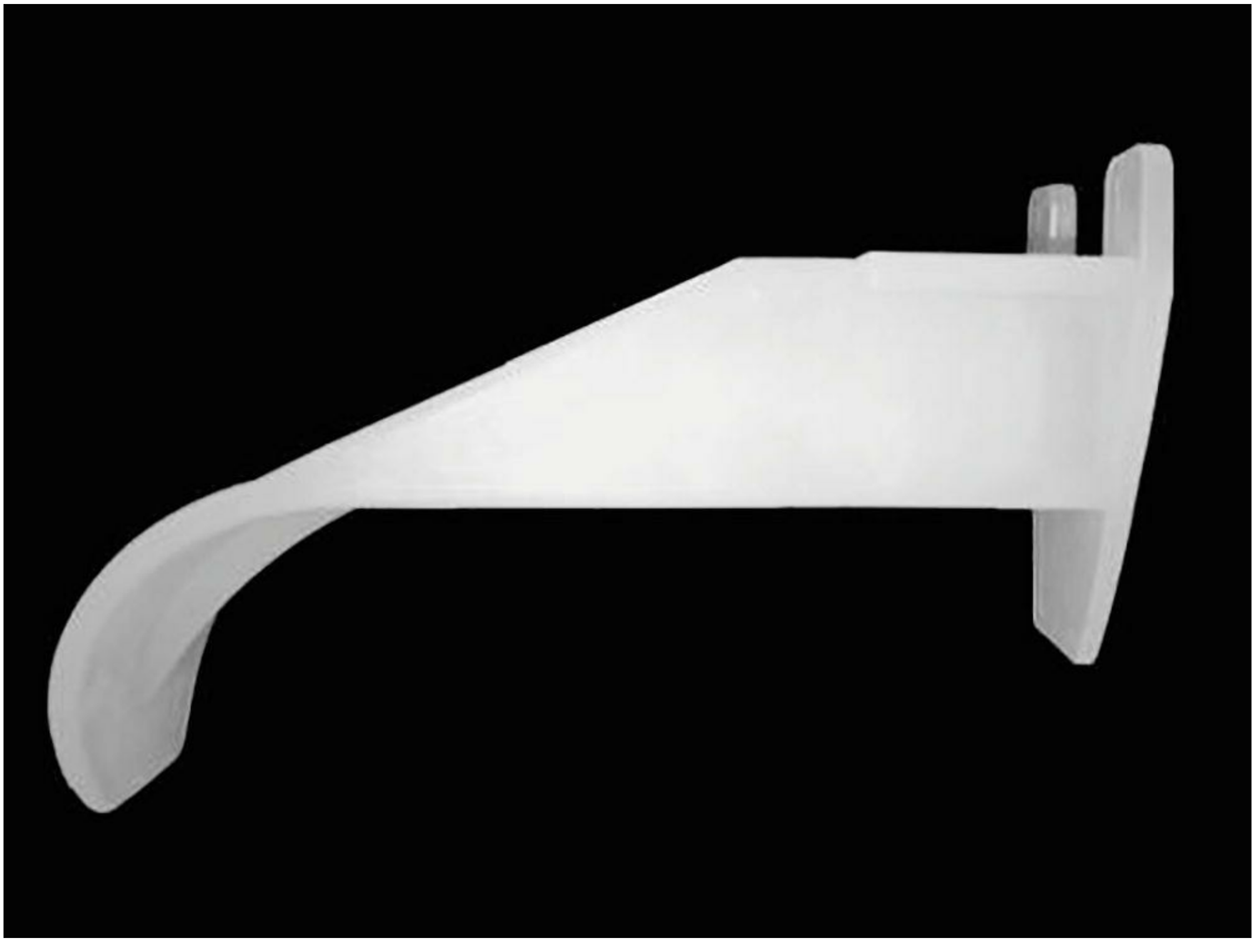


Figure 6.7. Modified Ovassapian airway.

Figure 6.8. Modified Ovassapian airway to increase mouth opening. (From Truong A, Truong DT. Use of a modified Ovassapian airway to increase mouth opening for fiberoptic or tracheal intubation in a patient with severe trismus. *Anesth Analg.* 2011;113(4):958–959, with permission.)

Unanticipated Difficult Intubation

Despite the multitude of schemes for airway assessment and prediction of difficult intubation, unanticipated difficulty with exposure of the larynx after induction of GA and muscle paralysis still sporadically occurs. Current airway assessment methods do not always reliably predict when the glottic opening can be adequately visualized by direct laryngoscopy. Furthermore, even if the glottis can be visualized with fiberoptic indirect laryngoscopy, it is not uncommon that tracheal intubation cannot be successfully achieved because of the nonlinear path from the operator's eyes to the larynx. Failed intubation attempts can deteriorate rapidly and suddenly to life-threatening "cannot intubate–cannot ventilate" disasters.[58] Preplanning with a backup strategy will help to avoid impulsive decision-making under severe

stress.[59,60]

After calling for expert assistance, the first priority should be to ensure adequate ventilation and oxygenation. If bag-mask ventilation is not adequate, a supraglottic device should be inserted to overcome oropharyngeal obstruction. Once ventilation and oxygenation are achieved, the second priority is to avoid further airway trauma that may precipitate complete airway obstruction. Intubation techniques selected for these difficult situations should have the least risk of trauma and high rates of success. Consequently, blind intubation techniques and repeated attempts using rigid laryngoscopy should be discouraged. A rational and orderly progression from the rigid direct laryngoscope to the video laryngoscope or flexible fiberoptic bronchoscope should be followed. In case fiberoptic bronchoscopy attempt also fails, it is important to resist the urge to revert back to rigid laryngoscopy. Failed intubation under these circumstances stems from increasing airway edema after each unsuccessful attempt. Each subsequent intubation attempt using the same technique will have even less chance to succeed than the previous one. To compound the difficulty, it becomes increasingly difficult to maintain adequate oxygenation. Rapid desaturation not only severely limits the time available to succeed intubation but also adds a terrifying sense of urgency while trying to perform a very difficult procedure. In our experience, the combined technique using the LMA, fiberoptic bronchoscope, and Aintree intubation catheter (AIC) is the safest and the best option to secure the airway. A well-seated LMA ensures adequate ventilation and oxygenation. A swivel adapter placed between the LMA and anesthesia circuit allows access to the trachea while ventilation through the LMA is continuously maintained. The AIC (Cook Medical, Bloomington, IN) is a modified airway exchange catheter with a larger internal diameter of 4.8 mm that is preloaded onto a pediatric bronchoscope. This bougie tube was designed specifically for use with a fiberoptic bronchoscope to facilitate endotracheal intubation through an LMA. The bronchoscope armed with the AIC is inserted into the LMA, and under direct vision, the glottic opening is identified, passing the AIC to the tracheal lumen. Using the AIC as a guide, the ETT is then advanced over the AIC into the trachea for intubation. This combined technique is our favorite approach when called to assist failed intubation. The greatest advantage is that ventilation is adequately assured during intubation attempts. Unlike other techniques, this combined approach takes advantage of the useful features of

multiple airway equipment. This technique is essentially atraumatic and does not lead to complete airway obstruction even during repeated attempts. Finally, the success for airway control is almost always assured. By bypassing oropharyngeal edema, the LMA not only ensures adequate ventilation but also allows effective suctioning of the supraglottic area and serves as a straight conduit leading to the larynx. Furthermore, by displacing away the surrounding edematous soft tissues, the elliptical rim of the LMA provides valuable exposure of the laryngeal inlet for easy bronchoscopic visualization of the vocal cords.

PERIOPERATIVE CARE OF PATIENTS WITH A LARYNGECTOMY STOMA

Occasionally, patients present for surgery with laryngectomy stoma. Often mistaken by anesthesia providers as a tracheostomy, a permanent stoma after total laryngectomy presents important perioperative implications for anesthesia. Because there is no longer a communication between the tracheobronchial system and the digestive tract, aspiration of gastric contents is physically impossible.[61] Regrettably, the ASA practice guidelines for preoperative fasting do not take this fact into consideration. Therefore, these patients are often subjected to unnecessary prolonged fasting before surgery.[62] In contrast, the risk of pulmonary aspiration of small objects into the stoma is often overlooked. Because of the large stoma opening with smooth downsloping rim contour, there is a significant risk of aspiration of foreign bodies by strong negative pressure generated during deep inspirations. Small foreign bodies such as vial covers and needle caps may be at risk of accidental inhalation into the trachea or lungs. Extra care should be taken by anesthesiologists in handling small objects in the vicinity of an uncovered stoma (Fig. 6.9). Many laryngectomees undergoing surgery also present with a tracheoesophageal prosthesis (TEP) for esophageal speech. If intubation is required, the TEP may either be removed or left in place. During insertion of a cuffed ETT into the stoma to enable positive pressure ventilation, utmost caution should be exercised to avoid dislodgment of the prosthesis. Finally, after extubation, it is necessary to check again with a bronchoscope to ascertain that the TEP is still in place. Accidental dislodgement and pulmonary aspiration of the voice prosthesis are not

uncommon and, if unrecognized, may result in serious complications.

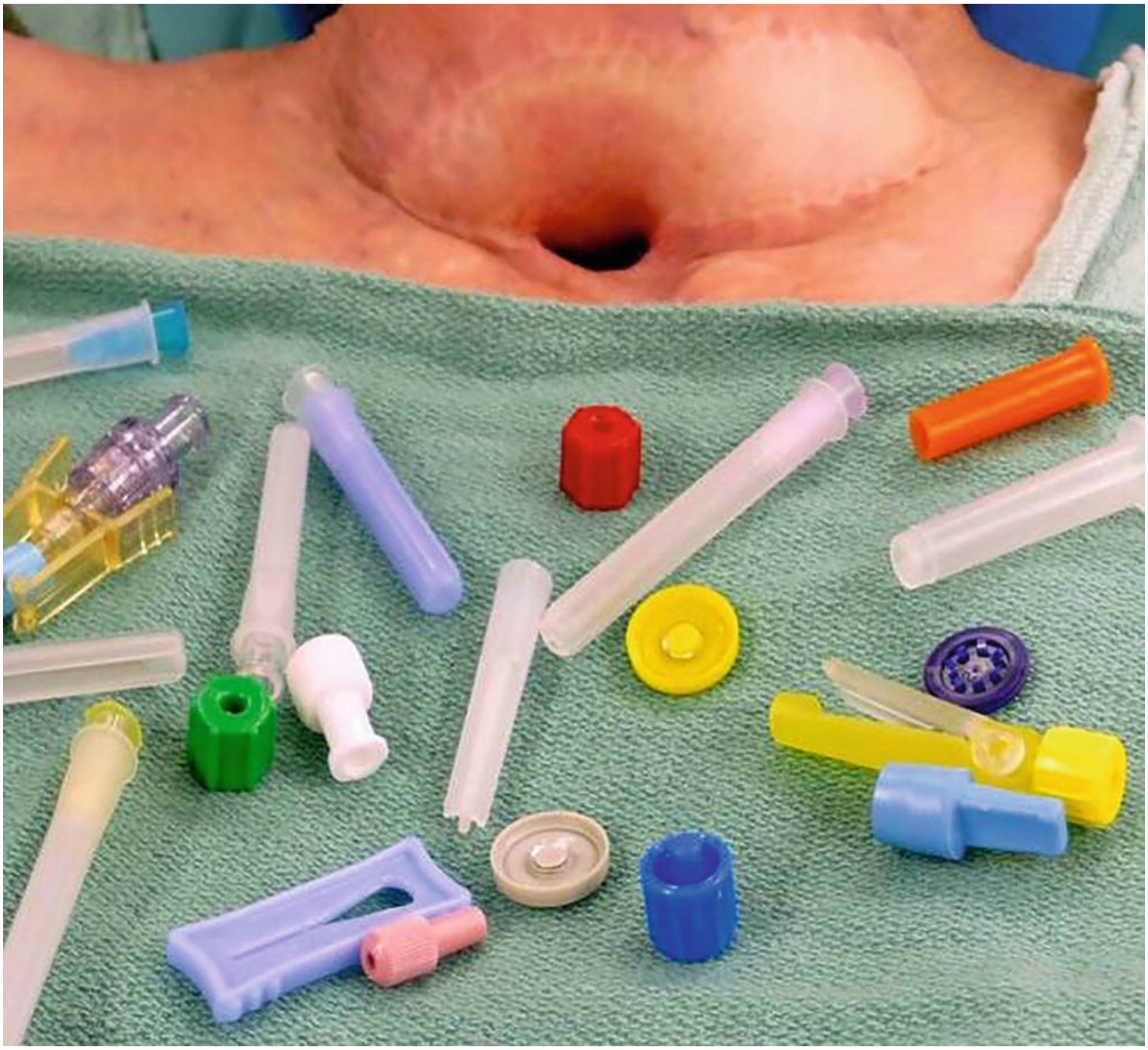


Figure 6.9. Stoma with objects.

INTRAOPERATIVE ANESTHETIC MANAGEMENT: VASCULAR ACCESS AND MONITORING

Vascular Access

For fluid and intravenous drug administration, peripheral vascular access for head and neck surgery is obtained by cannulation of an upper extremity vein with a large-bore catheter. A second peripheral intravenous catheter is usually inserted after induction in case the first peripheral line infiltrates or does not flow well after patient positioning with arms tucked at the sides. In the majority of cases, blood transfusion for combined head and neck and plastic reconstruction procedures may be given using a standard fluid warmer such as the enFlow fluid/blood warming system (GE Healthcare, Little Chalfont, UK). For cases with anticipated massive blood loss such as carotid body paragangliomas, a central venous catheter may be needed. The internal jugular and subclavian veins are common choices for cannulation. Catheters in these large vessels are often undesirable in head and neck surgery due to their intrusion into the surgical field. Femoral vein catheters offer the benefit of being far from the surgical field and also serve as a reliable central access in cases of surgical bleeding originating from the vessels of the neck. Rapid blood transfusion devices such as the Belmont Rapid Infuser (Belmont Instrument, Billerica, MA) are available to rapidly infuse blood at rates from 2.5 to 1,000 mL/min with the touch of a button.

Monitoring is an essential component of intraoperative anesthetic care. The standards for basic intraoperative anesthetic monitoring were established by the ASA in 2005.[63] Routine intraoperative electronic monitors include inspired oxygen concentration, pulse oximetry, end-tidal CO_2 by capnography, blood pressure, heart rate and rhythm, and airway pressure.

For hemodynamic monitoring, blood pressure measurements every 3 minutes with a sphygmomanometer are usually adequate for most cases. For long cases, the CNAP Monitor 500 (CNSystems Medizintechnik AG, Graz, Austria) allows noninvasive continuous beat-to-beat hemodynamic monitoring without the need for arterial cannulation. Based on the principle of arterial wall unloading, this monitor uses two finger cuff sensors wrapped around the index and middle finger to obtain a blood pressure signal that is calibrated using a special transfer function. After processing, the monitor provides a real-time continuous display of systolic, mean, and diastolic blood pressure, left ventricular stroke volume, and cardiac output and pulse pressure variability.

For patients with uncontrolled hypertension, congestive heart failure, or ischemic heart disease, invasive monitoring of the arterial pressure by an

indwelling arterial catheter is beneficial. Blood samples for determination of arterial blood gases, hemogram, and other blood chemistries can be taken from the arterial line. Complications from arterial cannulation such as ischemia and infections are fortunately rare.

Central venous pressure monitoring is useful to optimize blood volume status in patients with a history of congestive heart failure. Similarly, monitoring of pulmonary artery pressure and cardiac output with a pulmonary artery catheter is occasionally required for critically ill patients. These monitoring modalities are not practical for head and neck surgery. As an alternative to these invasive procedures, beat-to-beat left ventricular output and stroke volume can be measured much less invasively by arterial line tracing contour analysis. Complex computer algorithms serve to calculate the area under the systolic portion of the arterial pulse waveform. This technique has been shown to be accurate and reliable when compared to cardiac output measurements by a pulmonary artery catheter. This noninvasive technique is also useful in predicting the hemodynamic response to intravenous fluid administration. Cyclical fluctuations of the arterial blood pressure tracing related to the expiratory and inspiratory phases of the respiratory cycle have been used to detect hypovolemia when the difference is >10 mm Hg. Because low blood volume decreases right ventricular preload, increases right ventricular afterload, and decreases left ventricular afterload, a marked variability in stroke volume can be used as a predictor of responsiveness to fluid administration in low cardiac output states. Because the accuracy of this technique depends on the quality of the arterial waveforms, this technique is not reliable in the presence of frequent atrial or ventricular arrhythmias, especially atrial fibrillation. Intraoperative transesophageal echocardiography examinations routinely performed by cardiovascular anesthesiologists are seldom needed for head and neck surgery, except for very rare cases of cardiogenic shock.

Monitoring of Depth of Anesthesia and Brain Function

The concept of depth of anesthesia is fundamental to the science and art of providing GA. Yet, paradoxically, it is also the least well understood. Although GA first became widely practiced in late 1846, it took close to one century later in 1937 for Guedel to describe the four stages of anesthesia.[64] He based these four stages empirically on observed clinical signs such as loss

of consciousness, regular breathing, and eyelid reflex. This primitive and imprecise scheme often led to anesthetic overdose and terrifying intraoperative patient awareness and recall.

It was only in 1994 that the bispectral index (BIS brain function monitor, Covidien, Dublin, Ireland) was introduced to gauge the depth of anesthesia and to help adjust doses or concentrations of anesthetic agents accordingly to achieve optimal depth.[65] The goal is a plane of unconsciousness deep enough to prevent intraoperative awareness and light enough to allow rapid emergence from anesthesia. Using a complex algorithmic analysis of several electroencephalographic parameters, the BIS monitor provides a single dimensionless number ranging from zero to 100. A BIS value between 40 and 60 indicates an appropriate level of anesthesia. The BIS monitor probes must be applied on the patient’s frontal and temporal areas. For this reason, this monitor is not as commonly used in head and neck surgery compared to other surgical specialties.

Occasionally, a standard 19-scalp electrodes continuous real-time electroencephalogram EEG is needed for intraoperative monitoring of brain function. Typically, this is needed in cases presenting with high risk for intraoperative strokes such as complex surgical resection involving the carotid arteries or in patients with known critical carotid stenosis.

PATIENT POSITIONING FOR SURGERY

Patient positioning is intended to improve access of the surgeon to the target operative field. The desired position may impose potentially harmful anatomical and physiologic changes to the patient. Furthermore, patients are often placed in these positions after the induction of GA. The anesthetized and paralyzed patient may be subjected to exaggerated postures, which they would not be able to tolerate if they were awake. Therefore, there should be a compromise between surgical needs and patient’s ability to withstand the desired position. In doubt, before induction of GA, the patient should be allowed to assume the proposed position while still awake to assess the limits of his comfort. All pressure points and prominent bony parts, especially elbows and heels, should be free from direct contact with the cold steel

operating table. These vulnerable areas should be protected by careful padding with foam pads to prevent peripheral nerve injuries.[66] Injuries to the brachial plexus and its main branches, in particular the ulnar nerve, are best prevented by positioning the well-padded arms, elbows, wrists, and hands comfortably tucked alongside the trunk. In large patients, a well-padded arm protector toboggan can be placed to protect the arms from being leaned upon by surgical assistants. Leg compression devices should be applied for thromboprophylaxis. The operating room table is often turned 90 or 180 degrees from the anesthetic machine to allow free access around the head and neck not only for the attending surgeon, but for all the surgical assistants. The patient is usually positioned in the supine position with the back of the table elevated 30 degrees to improve surgical access. Elevation of the head and thorax shifts abdominal contents away from the diaphragm, decreases atelectasis of the lower lobes of the lungs, and improves functional residual capacity. It also facilitates venous drainage away from the operative site, resulting in a less bloody operative field and decreased tissue edema. Side effects include decreased cerebral perfusion, risk of air embolism, and concealed blood loss trickling down unnoticed under the surgical drapes. When neck extension is needed to improve surgical access, mechanical compression of the carotid sinus located at the bifurcation of the common carotid artery may lead to the carotid sinus reflex. Stimulation of the vagus nerve precipitates bradycardia or asystole. In patients with carotid sinus hypersensitivity, this reflex is greatly exaggerated and can be triggered by simple extension of the neck without direct manual compression of the carotid sinus.[67]

SPECIAL INTRAOPERATIVE AIRWAY MANAGEMENT

Laser Surgery

By focusing the laser beam impact on a tight pinpoint target, laser surgery confers many important advantages: precise surgical resection, preservation of neighboring tissues, and less bleeding and tissue edema. The most widely used laser in head and neck surgery of the upper airway is the carbon dioxide (CO_2) laser. It can be used either to cut or to vaporize the lesion depending on

the laser settings. It is especially useful in resecting bulky tumors of the epiglottis and vocal cords. The Nd:YAG laser transmitted by fiberoptic cables is more flexible and better adapted to tumors of the lower airway. Surgical lasers have the potential for inadvertent tissue damage and for causing fires. Eye injuries vary depending on the depth of penetration of the beam. CO_2 lasers cause corneal injuries, whereas Nd:YAG lasers can damage the retina. The eyes of the patient must be protected with moist eye pads or special laser eye covers. As oil-based ointments are flammable, water-soluble eye ointments should be used. To prevent sudden patient movement and inadvertent impact of the beam, muscle relaxation is usually required to help ensure an immobile surgical field. The laser beam like any light beam can be deflected. Instruments with a polished surface can reflect laser beams to an unintended destination and thus cause injury, especially to eyes of operating room personnel. Protective goggles should be worn by everyone in the operating room. A clear warning sign of laser use must be posted on the operating room door. Equipment and instruments inside the room should have nonreflective surfaces.[68] To prevent fire in the upper airway, the lowest inspired concentration of oxygen should be delivered, ideally not higher than 30%. Nitrous oxide also should not be used because it supports combustion.[69] Laser vaporization of tumors, especially from CO_2 lasers, often results in a plume, which contains not only smoke and particulate debris but also cancer cells, viruses, and carcinogens. A smoke evacuator system with a high-efficiency particulate air filter should be positioned at the surgical site. Specially designed laser plume face masks should be worn. A protocol to manage airway fire should be in place and periodically reviewed and rehearsed. In the event of airway fire, positive pressure ventilation should be stopped immediately to prevent fanning the fire down the tracheobronchial tree. The burning tracheal tube should be removed and any fire should be extinguished with water. Intravenous dexamethasone should be administered to reduce airway edema. Complications related to laser surgery are potentially catastrophic. They are also highly preventable. Consequently, all the precautions about laser safety should be scrupulously adhered to by all personnel involved.

Tracheal Resection and Reconstruction

Management of the airway for tracheal resection is one of the most formidable challenges in anesthesia practice.[70] Airway obstruction caused by the tracheal lesion, the differences in location of the segment to be resected from the cricoid to the carina, and the various phases of the resection and reconstruction require different techniques of airway control. Depending on the degree of airway obstruction, an intravenous, inhalational induction, or awake intubation may be selected. After ensuring adequate ventilation, a diagnostic flexible bronchoscopy should be performed to assess the involved segment and decide on the best way to secure the airway. Once the trachea has been transected, the most popular option for intraoperative ventilation involves distal tracheal intubation and cross-field ventilation. For lesions involving the upper and middle trachea, the tracheal tube is pulled back above the segment to be resected while still kept in the tracheal lumen. The surgeon inserts a second, sterile, flexible wire-reinforced tube through the surgical field into the distal trachea. This tube is connected to the anesthesia circuit to continue intermittent positive pressure ventilation. After resection of the diseased tracheal segment, the tube is removed during short apneic periods to allow completion of an end-to-end tracheal anastomosis. The main advantage of this technique is simplicity and safety. The drawback is the presence of a tube inside the trachea interfering with the completion of the tracheal anastomosis.

If concern exists that a tracheal tube may interfere with delicate surgical exposure, manual low-frequency jet ventilation may occasionally be needed.[71] After the trachea is transected, a long jet ventilation catheter inserted through the lumen of the tracheal tube and positioned in the distal trachea is attached to an oxygen source with outlet pressure of 50 psi. Ventilation is achieved by manual triggering. The oxygen concentration is diluted by entrained air following the Venturi principle. The most important advantage of jet ventilation is to allow ample room around a small catheter for the surgeon to perform tracheal anastomosis. Potential drawbacks include whipping motion of the catheter tip, inadequate ventilation and oxygenation, and entrainment of blood and tissue debris into the distal tracheobronchial system. High-frequency jet ventilation and high-frequency positive pressure ventilation[72] are generally not needed for tracheal resection performed by

head and neck surgeons. At the conclusion of surgery, emergence and extubation constitute the most critical steps of the entire anesthetic. It requires meticulous planning and execution through collaborative efforts between surgeon and anesthesiologist. Long-acting narcotics should be avoided. Neuromuscular blockade effects should be fully reversed. Every effort should be made to extubate the trachea to avoid trauma to the tracheal anastomosis by the tracheal tube and its cuff during mechanical ventilation. A guardian stitch placed between the chin and the chest helps keep the neck flexed and prevents traction on the tracheal anastomosis.

ANESTHETIC AGENTS OR TECHNIQUES AND TUMOR RECURRENCE

Cancer recurrence and metastases constitute major concerns in the treatment and survival of cancer patients. Recently, investigative reports suggest that certain perioperative factors including anesthesia techniques and analgesic drugs may have direct effects on cancer cells and patient cell-mediated immunity, contributing to recurrence and metastases.[73] Consequently, there is a strong stimulus to identify these factors and develop better modalities of anesthesia care with the aim of lowering rates of recurrence. The basic process of recurrence involves the complex interaction between the propensity of cancer cells to grow and the host defenses against cancer cell proliferation. The mechanisms by which perioperative factors may influence cancer cell growth and the host immune response are multifactorial, complex, and not yet completely understood. Surgery itself, the use of blood products, postoperative pain, and inadequate pain relief have been known to promote tumor growth by stimulating the cytokine stress response and suppressing cell-mediated immunity. For these reasons, adequate relief of pain is essential. The drugs most commonly used to relieve acute pain following surgery are opioids. Unfortunately, opioids have also been shown to exert deleterious effects by inhibiting host humoral and cell-mediated immunity.[74,75] Morphine has also been shown to stimulate tumor cell migration and proliferation in human endothelial cells in vitro. Avoiding opioids by using alternative pain management strategies may positively

impact cancer recurrence. However, although single-dose or low-dose opioids can promote tumor growth, extended exposure to high concentrations may suppress tumor growth.[76] In contrast, in addition to the relief of pain, local anesthetics may also exert cytotoxic effects on cancer cells. Lidocaine and bupivacaine have been shown to inhibit stem cell division and growth in vitro.[77] Regional anesthesia techniques such as epidural and spinal anesthesia have been widely used for various types of cancer surgery because they provide excellent analgesia, attenuate the stress response, and preserve the integrity of the host immune system. These techniques have been reported to be associated with a decrease in recurrence in certain types of cancers.[78] For the same reasons, paravertebral blocks have become very popular for breast surgery. For head and neck cancer surgery, superficial cervical plexus blocks have been performed for analgesia for thyroidectomy. In a recent report, cervical epidural anesthesia was associated with increased cancer-free survival in laryngeal and hypopharyngeal cancer patients.[79] Owing to their effects on COX2 and PGE2, which are major mediators in cancer progression, nonsteroidal anti-inflammatory drugs have a strong potential anticancer effect.[80]

Intravenous induction agents such as thiopental and ketamine have been shown to suppress NK cell activity in an inoculation animal model of breast cancer, which resulted in an increase in metastases.[81] In contrast, propofol may exert an antineoplastic effect by decreasing the production of PGE2 by monocytes in vitro.[82] Potent inhalational agents such as isoflurane, desflurane, and sevoflurane have been associated with immune modulation and potentially increased tumor metastasis in vitro and in experimental animal models.[83] Finally, perioperative allogeneic blood transfusion has been linked to immunosuppression, inflammatory response, and cancer recurrence.[84] Most of these reports come from laboratory experiments and retrospective clinical studies. Until randomized clinical trials are able to support a causal link between a particular anesthetic agent or technique to cancer recurrence, it is premature to introduce changes to the current standards of anesthetic care.[85] For the time being, the traditional high standards of anesthesia practice should focus on minimizing preoperative anxiety, achieving optimal anesthetic depth to blunt the surgical stress response, and providing excellent relief of pain in the postoperative period.

Patients undergoing extensive surgical procedures are susceptible to

major intraoperative blood loss requiring transfusion of blood and blood products. Unfortunately, in cancer patients, blood transfusions may be associated with transfusion-related immunosuppression, inducing tumor growth and causing recurrence. Findings of studies investigating the association between blood transfusion and cancer recurrence differ widely depending on the type of cancer studied. On one hand, perioperative blood transfusions have been linked to cancer recurrence and cancer-related mortality in colorectal carcinoma,[86] hepatocellular carcinoma,[87] pancreatic carcinoma,[88] and lung cancers.[89] On the other hand, studies investigating ovarian, renal, and bladder cancer surgeries show conflicting and inconclusive results regarding blood transfusion as an independent risk factor for recurrence.[90] Finally, patients who received allogeneic blood transfusion for prostate cancer surgery did not have a higher risk for cancer-related deaths as compared to nontransfused patients.[91] With regard to patients with cancers of the head and neck necessitating complex reconstruction after resection, transfusion of blood is often required to maintain perfusion of microvascular free tissue flaps. At the present time, there are no published studies that specifically focus on head and neck cancer surgeries and cancer recurrence after blood transfusion. Studies in this area are definitely warranted.

Emergence and Tracheal Extubation

At the end of surgery, anesthetic goals include a smooth emergence and timely extubation to avoid gagging and bucking on the tube. Even when the surgery procedure does not involve the airway, extubation carries more risks than intubation.[92] The main risk factors for problems at extubation are preexisting difficult airway, residual effects from muscle relaxants and narcotic analgesics, and airway edema. The incidence of reintubation is higher for laryngoscopy and panendoscopy.[93] In surgery involving the oropharyngeal cavity or the larynx causing airway edema or vocal cords paralysis, the risk of reintubation is 1% to 3%, a 10 fold increase compared to surgery not involving the airway.[94] Furthermore, reintubation under these circumstances can be very challenging or even impossible. In case of failed extubation, devices to assist ventilation such as extraglottic devices may not function adequately due to edematous and distorted airway anatomy. Extubation of the difficult airway should be given as much attention as

intubation. The following criteria are sought for extubation: patient awake, comfortable, following verbal commands, and demonstrating adequate tidal volume, respiratory rate, peak inspiratory force, and sustained head lift. In cases of high-risk extubation, it is important to discuss extubation plans with the surgeon. If laryngeal edema is suspected, it is essential to ensure airway patency before extubation by performing the cuff leak test.[95] After deflating the tracheal tube cuff, the ETT lumen is occluded and the patient is asked to breathe in and out deeply. An audible air leak around the tube indicates that there is adequate flow of air around the tube and the airway is patent. If there is any doubt, especially in cases of potential vocal cord paralysis secondary to recurrent nerve injury,[96] a trial extubation can be performed. A hollow jet ventilating tube changer (Cook Airway Exchange Catheter Cook Critical Care) is inserted through the tracheal tube, the cuff of the ETT deflated, and the ETT withdrawn while the exchanger remains inside the tracheal lumen. The lumen of these hollow tubes can be used to insufflate or ventilate the patient with oxygen. If necessary, the exchanger can be used as a guide to reintubate the patient.

AIRWAY MANAGEMENT IN DEEP NECK INFECTIONS AND POSTOPERATIVE NECK HEMATOMA

The management of these life-threatening airway emergencies follows the same general principles. An enlarging neck mass compresses and distorts the airway and may progress rapidly to complete airway obstruction. In retropharyngeal abscess, there is the added risk of rupturing the abscess and pulmonary aspiration of purulent material during manipulation of the airway.[97] The techniques used to secure the airway must be carefully individualized, based on the anticipated difficulties and the expertise of the attending anesthesiologist and head and neck surgeon. Minor neck bleeding can be treated expectantly. Early deep neck infections can be treated with antibiotics and close observation. Even when surgery is indicated, an intravenous induction, laryngoscopy, and intubation may be considered in the following circumstances: early diagnosis, minimal neck swelling, no stridor, no trismus, and a normal airway without anticipated risk for difficult

ventilation and intubation.

In contrast, increasing stridor may signal impending complete airway obstruction. In the case of postoperative hematoma, because of the large mass under the mandible and severe edema of the epiglottis and vocal cords, airway anatomy becomes distorted, displaced, and narrowed. Ventilation and intubation, which were easy earlier during the initial induction of anesthesia, may become very challenging. Bag-mask ventilation and transtracheal surgical airway can be extremely difficult or even impossible.[98] The patient should be brought to the operating room as expeditiously as possible. A coordinated effort should be made to assemble equipment needed: anesthesia emergency airway cart and surgical airway equipment including cricothyrotomy, jet ventilation, and tracheostomy sets. Anesthesiologists and surgeons with special expertise in emergency airway management should be called for assistance. The decision to proceed with awake FOI versus awake tracheostomy should be made carefully taking into consideration the urgency of the situation and the expertise and skills of the attending physicians involved.[99] Under these circumstances, only operators with special expertise in dealing with critical airway emergency should attempt awake FOI after topical anesthesia of the airway. It is important to reassure the patient and explain the successive steps of the procedure and their rationale. To ensure adequate spontaneous breathing, the patient should be kept awake by avoiding sedatives, hypnotics, and muscle relaxants. It is imperative to avoid airway trauma from rigid laryngoscopy, which can precipitate complete airway obstruction. Even without intravenous sedation, complete airway obstruction during application of topical airway anesthesia may occur.[100] Consequently, the surgeon and surgical team should be scrubbed, gowned, and ready to perform emergent cricothyrotomy or tracheostomy. Because of copious secretions, pretreatment with anticholinergic agents may be needed, and it may take longer to achieve optimal conditions for intubation. Localization of the glottic opening may be facilitated by delivering high flows of oxygen through the fiberoptic bronchoscope to disperse secretions. A reasonable time limit and number of intubation attempts should be set. It is advisable to proceed immediately to awake tracheostomy under local anesthesia before complete airway obstruction occurs. Success in these difficult conditions requires the expertise of an experienced and skillful head and neck surgeon. In case of loss of airway during tracheostomy, an

extraglottic device should be placed for rescue ventilation to allow the surgeon to successfully complete the procedure.[101]

SUMMARY

Anesthesia for head and neck cancer surgery presents unique challenges in all aspects of anesthetic care and during all stages of the perioperative period. Thorough preoperative evaluation and expert consultation for assessment of serious comorbidities are crucial to optimize the patient’s clinical status before surgery. The major intraoperative concern is control of the airway not only during induction, intubation and throughout the entire surgical procedure but also at emergence and extubation. A difficult airway related to invasion of the airway by malignant tumors is unquestionably the most challenging airway encountered in anesthetic practice. A complete airway assessment should focus not only on the well-recognized causes of difficulties but also on the implications of the cancer, previous resections, and radiotherapy. Potential airway problems should be anticipated not only when the patient is awake but also after induction of GA. The surgeon should be involved through communication and discussion to formulate a comprehensive collaborative plan of action. In case of failed intubation, the first priority is to preserve the ability to ventilate. It is imperative to refrain from repeated traumatic intubation attempts because the ensuing airway edema and bleeding will lead to sudden and catastrophic loss of airway. Expert help should be summoned early to successfully manage potentially lethal “cannot intubate–cannot ventilate” scenarios. Improvement of professional competence through continuing education, practice, and learning new techniques ensures proficiency in managing the most challenging airways.

Anesthesia practice devoted mainly to surgery for head and neck cancers yields many important benefits. First, the expertise acquired through routinely managing difficult airways confers competence in the most vital area of anesthesia practice. Head and neck anesthesiologists are often called upon to assist with difficult airways encountered in other surgical specialties. Furthermore, in case of an unanticipated airway crisis, the best assistance an anesthesiologist can receive is from the head and neck surgeon who is

already present in the same operating room. There is no need to call for outside help and no precious time is wasted. Compared with surgeons from other specialties, head and neck surgeons are highly skillful in the procedures anesthesiologists perform to secure the airway, especially rigid laryngoscopy and flexible bronchoscopy. The timely establishment of a surgical airway through urgent cricothyrotomy or tracheostomy may mean the difference between life and death. Finally, as research findings concerning potential associations between anesthesia agents and cancer recurrence begin to emerge, these results should be taken into account and incorporated into daily anesthesia practice. Hopefully, high standards and up-to-date anesthetic care will contribute to favorable outcomes, not only during the perioperative period but also to the long-term survival of head and neck cancer patients.

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7 Head and Neck Cancer Care: Quality Guidelines

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The quality and appropriateness of cancer care are of paramount importance and can critically impact outcome. Deviation from evidence-based care will result in higher treatment costs and may jeopardize patients' outcomes. Providing evidence-based care should provide the patient the best opportunity for cure. Failure of initial treatment is associated with diminished tumor control and survival regardless of salvage treatment.[1,2] Quality of care has been defined as delivering efficient evidence-based care by experienced clinicians in an accessible setting or as doing the right thing, for the right patient, at the right time, and achieving the best possible result.[3]

The 2001 report by the Institute of Medicine (IOM) entitled "Crossing the Quality Chasm: A New Health System for the 21st Century" highlighted the gap that exists between what we know to be effective, beneficial care, and the care that is often delivered to an individual patient.[4] In the report, the IOM stated, "Between the health care we have and the care we could have lies not just a gap, but a chasm." The report, signifying a national initiative to improve the quality of care in the United States, articulated the following 6 aims for a new health care system: (1) enhance the safety of health care by avoiding injuries to patients; (2) provide effective services based on scientific knowledge (evidence-based care) and avoid services of no proven benefit; (3) deliver patient-centric care; (4) deliver timely care by reducing wait times and harmful delays; (5) increase efficiency and decrease waste; and (6) deliver care that is equitable regardless of gender, ethnicity, and social economic status. The IOM also recognized a need to optimize quality cancer care in the United States and recommended funding research into factors

influencing care and the quality of cancer care delivered.[5]

The United States spends the most money per capita for health care delivery of any country in the world, yet our outcomes are not outstanding. It is estimated that patients receive evidence-based care only 50% of the time, leading to increased cost of care.[5] In the United States, health care costs continue to rise but at a less rapid rate. In 2013, hospitals received an increase of 4.3% to $936.9 billion compared to 5.7% growth in 2012.[6] Payments to physicians and clinical services provided increased 3.8% in 2013 to $586.7 billion, from 4.5% growth in 2012. Medicare outlays accounted for 20% of national health spending in 2013 and grew 3.4% to $585.7 billion, down from a growth rate of 4.0% in 2012. Cancer care costs will continue to increase for the foreseeable future due, in large part, to aging “baby boomers” who are in their cancer-prone years and the introduction of new technologies and molecularly targeted therapies.[7] The Affordable Care Act (ACA) is an attempt by the federal government to diminish the rate of increase while at the same time improving the quality of care provided to patients.

An example of methodologies within the ACA designed to decrease the cost of care includes alternative payment strategies; principal among these is value-based reimbursement.[8,9] Value in health care is defined as the outcome achieved (quality) divided by the cost of care to achieve that outcome.[10] Health care reimbursement is currently tied to the quantity and volume of care delivered rather than outcomes. Payers, the largest of which is the Centers for Medicare and Medicaid Services (CMS), are moving toward value-based reimbursement as a way of rewarding providers (hospitals and health care professionals) that achieve better outcomes. It is estimated that one-third or more of health care dollars expended caring for cancer patients are wasted on inappropriate or futile care.[5] Examples include inappropriate or poorly performed surgical procedures, care not consistent with current cancer therapeutic guidelines, or continuing to administer chemotherapy in the terminal phase of cancer illness when end of life and supportive care is more appropriate.

One of the difficulties in improving the quality of care for patients with cancer of the head and neck is a lack of available benchmark or comparator data; capturing outcome data is difficult and costly. Current electronic health records (EHR) do not facilitate capturing important data elements related to a

specific patient that can be easily retrieved for reporting and analysis. As the EHR evolves, patient information such as demographics, tumor-specific details, comorbidity, the treatment provided, and functional outcomes will be captured as discrete data elements in the workflow, thus facilitating reporting outcomes. As these databases become robust, risk-adjusted outcomes along with the cost of care will be reportable. At that point, value analysis based on high-quality data will be reportable allowing for benchmarking outcomes and the ability to compare individual providers and institutions.

Although the promise of the EHR to support these goals remains in the future, there are tools available now to improve the quality head and neck cancer care and to potentially diminish costs of care. Diminishing variability through the use of cancer care pathways is one readily available resource. The National Cancer Center Network (NCCN) has developed and refined treatment guidelines for patients with cancer of the head and neck based on the highest level of evidence available with input from a panel of cancer care specialists who are leaders in their respective fields of surgical, radiation, and medical oncology.[11] The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) and the American Head and Neck Society (AHNS) continue to develop clinical practice guidelines (CPGs) and quality measures to aid in the treatment of diseases of the head and neck and also provide tools for assessing the quality of care delivered. Currently, payers use cancer care guidelines as a resource for approving diagnostic studies and proposed therapy. Treatment falling outside of these guidelines may be denied reimbursement. In the future, it is anticipated that payers will direct patients with complex diseases to providers and institutions that can demonstrate value-based care.[12]

This chapter reviews current methodologies for capturing treatment outcomes and systems-based approaches for improving cancer treatment that include organization and structure of the multidisciplinary team, the use of evidence-based guidelines, coordination of care among the disciplines, process metrics supporting efficiency, and quality improvement tools.

Evidence-Based Clinical Practice Guidelines

As medical science and technology advance at a rapid pace, it has been a challenge for hospitals and medical providers to consistently provide high-

quality care to all patients. Difficulties in achieving this goal stem from our inability to clearly define quality metrics. To improve the quality of care patients receive, the IOM has challenged the health care community to incorporate evidence-based treatment guidelines as a way of consistently providing the best care possible for patients with complex or chronic disease. Patient care should be based on a continuous healing relationship customized to the patient's needs and values and oriented toward a common goal. The patient should have access to all relevant medical information in order to make informed decisions. All medical decision making should be evidence based, cooperative, and transparent. In addition, the health system should be safe, continually trying both to decrease variation and waste and to anticipate the needs of the patients.[4]

Meeting these goals is a great challenge, for all providers at all levels of the health care system. One way of improving the consistency and reducing the variation of health care delivered is through the development of structured treatment pathways that provide evidence-based evaluations and interventions to optimize the use of resources and deliver the best outcome.[4] CPGs are an important and powerful tool for assisting individual practitioners in using the most current evidence and consistent methodology available.[13] As many organizations attempt to incorporate guidelines as a strategy to reach the goals articulated by the IOM, an important tool has been the development of CPGs that are specific to a patient and disease population. This section will define the role of CPGs as a means to improve current quality standards of medical care. In addition, it will discuss the necessary rigor critical to creating clinically relevant evidence-based guidelines and how they contribute to improved cancer care.

Definition of Clinical Practice Guidelines

The IOM has defined CPGs as statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and assessment of the benefits and harms of alternative care options.[14] It has defined best practice standards for the CPG development. These include the following:

1. *Establishing transparency*: The fundi ld be publicly detailed.
2. *Management of conflict of interest*: Conflicts of interest should be limited,

and avoided, with group members divesting themselves of such conflicts when possible. When not possible, these conflicts should be fully disclosed.

3. *Guideline development group composition*: The group should be multidisciplinary with public and patient involvement.
4. *Clinical practice guideline–systematic review intersection*: Those performing systematic reviews and those in the guideline group should agree on the scope, method, and anticipated output of each group's work.
5. *Establishing evidence foundations for and rating strength of recommendations*: Each recommendation should be accompanied by an explanation with summary of the evidence, a confidence rating, and a strength rating.
6. *Articulation of recommendations*: Recommendations should be clear, provide direction, and be worded appropriately.
7. *External review*: External reviewers should comprehensively represent relevant stakeholders, and all reviews should be kept confidential.
8. *Updating*: CPGs should be regularly reviewed and updated.

Once developed, a CPG is rigorously evaluated for inclusion in the National Guideline Clearinghouse (NGC) database.[15] The NGC is an initiative of the Agency for Healthcare Research and Quality (AHRQ), an organization within the U.S. Department of Health and Human Services. Its mission is to provide physicians and other health professionals, health care providers, health plans, integrated delivery systems, and purchasers an accessible mechanism for obtaining objective, detailed information on CPGs and to further their dissemination, implementation, and use.[15] The NCG is an extensive collection of CPGs for a broad variety of medical conditions.

CPGs should contain systematically developed statements that include recommendations, strategies, or information that assists health care professionals to make decisions about health care in specific circumstances. All of these guidelines are evidence based, providing corroborating documentation from a systematic literature review.[16] It is important to recognize that guidelines are not to be used for reimbursement, health care rationing, legal precedents, and measures for licensing or certification or for cookbook medicine.

Within oncology, the NCCN establishes CPGs for cancer management. NCCN guidelines are compiled by an expert panel of radiation, medical, and

surgical oncologists who review current literature and make management recommendations based upon the best available evidence. Where evidence is lacking, expert consensus, with multidisciplinary representation from leaders in each field, is rendered.

Why Use Clinical Practice Guidelines?

There is currently a strong initiative to identify metrics that demonstrate quality care; more efficient care will reduce health care costs. The CMS has defined health care efficiency as the absence of waste, overuse, misuse, and errors through the limitation of unexplainable practice utilization variation.[17] CPGs are tools that can be used to improve patient care and clinical outcomes with the goal of providing safe, consistent health care that can be tailored to each patient’s clinical and personal situation.

Opponents to CPGs express concerns that these remove the individual decision making of the medical professional. However, CPGs are not intended to dictate care but are created to serve providers; in the setting of an ever-increasing body of literature, CPGs outline best practices based upon the best available evidence. Put another way, CPGs are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific individual circumstances.[17] They are not intended to supersede professional judgment and should allow for treatment options based on the variation in patients’ specific needs and interests.[18] The primary goals for CPGs are to minimize harm, reduce inappropriate provider variations in clinical care, and optimize health outcomes. Although the use of CPGs may result in reduction of costs, the financial benefit is not the main objective of an evidence-based guideline but merely a reflection of more efficient care.[16]

Process for Developing Clinical Practice Guidelines

CPG development has been refined over the years to be more standardized, thereby producing more reliable CPGs. When created with high methodologic rigor, a well-designed CPG can demonstrate the capacity of an organization or society to influence both patient health and public policy.[16] In general, the overall process needs to involve a systematic method of identifying evidence and ranking the relative strengths and quality of the

literature, which is then critically evaluated by a panel of experts to reach an agreement on the strength of a recommendation.

Because not every clinical question can be effectively answered by strong published evidence, there are three different approaches to constructing a CPG. The first is an informal consensus in which a panel of experts convenes to consider clinical questions and render a statement on best practices; this is done when strong evidence is lacking. The second is a formal consensus guideline for which a panel of experts considers clinical questions and renders a statement on best practices; this type does include a full formal review of the literature. However, due to gaps in the evidence, it may not be possible to link each individual recommendation to the evidence. In this situation, it may be necessary to produce a summary statement globally supported by the literature. The third method includes evidence-linked construction in which a comprehensive and systematic evidence search is performed. There is a formal ranking of the strength of the evidence through grade assignment. Each clinical recommendation is then linked to the supporting evidence and the strength for which the recommendation is supported by the evidence is defined. The latter is the most rigorous approach to developing CPGs, which represent the most complete evidence-based best practices; however, the process is often complex, time-consuming, and even inefficient.[16]

Within the surgical specialties, the AAO-HNS has been at the forefront of CPG development. This association has been interested in identifying high utilization and multidisciplinary clinical situations for which there needs to be clarification and standardization in otolaryngology practice. With the desire to produce high-quality CPGs, the AAO-HNS created a manual for guideline development[16] and assigned a task force to oversee the processes. This Guideline Development Task Force (GDTF) is made up of representatives from each sister society (e.g., AHNS) and receives input from all areas within otolaryngology. Through the GDTF and AAO-HNS leadership, otolaryngology has produced 13 CPGs and has more than 10 under development.

There are five basic steps for successfully creating a valid evidence-based guideline. First, the subject area must be identified and refined. Then, the guideline development group convenes and a systematic literature review is performed to assess the available evidence. The evidence is then translated

into recommendations. Lastly, the guidelines should be sent for external review.[19] The following steps outline the AAO-HNS process for producing a high-quality CPG.

Planning

The first step in guideline development is to define a topic that is timely for all of the stakeholders, including health care providers, patients and their families, society organizations, and even payers. The topic should be important and feasible. There should be multidisciplinary appeal, high utilization, or substantial burden of illness or cost due to the variation in care. A good topic also will have high-quality evidence available in the literature. It is also important to know if there are already existing published guidelines on a similar topic. During this phase of development, the guideline development group, including both the leaders and the outside stakeholders, should be identified. All conflicts of interest should be disclosed and addressed.

Evidence Collection

The initial topic may start out being very broad, but after an appropriate search of the literature, it may be refined to answer more specific questions. The target audience should be defined, as well as the types of practice settings in which the CPG would be applied. The group should discuss the clinical interventions as well as the outcomes that should be considered, including new technology and medications. With that information, it is possible to begin a literature search using identified keywords from such common sources as MEDLINE, Cochrane Community, etc.

Key Statements

Once the evidence has been defined, the key statements can be developed. These boldface statements are different from the global topics in that the latter often reflect controversy, practice variation, and areas for quality improvement. The key statements are more focused and describe when, who, what, and to whom each recommendation applies (i.e., under what conditions a provider would do a certain action to which patients). These statements use an action-type verb requesting the provider to perform a measureable action.

Examples would be “prescribe,” “perform,” “educate,” “test,” “dispose,” and “refer.” A key statement should avoid passive verbs such as “consider” when making a recommendation. There are times when a recommendation is vague, but the rationale for this, such as insufficient evidence, inability to reach a consensus, legal standard of care, economic prohibitions, and ethical constraints, must be included. After the key statements have been identified, each must be supported by text that summarizes the evidence. This text should describe the risks, harms, benefits, costs, and alternatives for the recommendation.

At this point, the evidence is reviewed to identify the strength of the recommendation. Using the evidence grading system described in GRADE,[19] the evidence can be ranked from A to D. A statement receiving Grade A evidence is strong enough that further research is very unlikely to change the confidence in the estimate of effect. The evidence supporting a Grade A is usually randomized controlled trials or diagnostic studies on specific or relevant populations. Grade B evidence indicates that further research is likely to have an important impact on the confidence in the estimate of effect and may even change the estimate. This type of evidence often comes from randomized controlled trials or diagnostic studies with minor limitations. A Grade C evidence recommendation is supported by evidence in which further research is very likely to have an important impact on the confidence in the estimate of effect; more studies are likely to change the recommendations. This is seen with statements based largely on observational studies. Lastly, a Grade D recommendation is one that is not supported by the evidence. In this setting, any estimate of effect is very uncertain and is usually based on expert opinion and case reports.[19]

The key statements, once completed, should contain a recommendation supported by graded evidence. In general, when a strong treatment recommendation can be made with Grade A evidence, it is also important to clearly state that the benefits of the recommended therapy exceed the potential harms. On the other end of the spectrum, providing an option within a Grade D recommendation indicates that the evidence did not describe a clear advantage to use one treatment over another, so other factors, such as patient preference and cost, must be considered. It is important to clarify that there is no evidence demonstrating that the benefits outweigh the harms when choosing one treatment over the others. When there is no recommendation

stated, there is a lack of evidence to guide a decision and to define the risk/benefit ratio. According to AAO-HNS guidelines, the recommendation is followed by supporting text, which discussed the level of evidence, benefits, harms, costs, values, and policies surrounding it.[16]

External Review

After the guideline is created, it must undergo an external review. This includes peer reviewers and relevant stakeholders. The reviewers scrutinize the CPG, focusing on the validity, the reliability, and the feasibility of the statements. In addition, the guideline should be reviewed by the board of any sponsoring organizations. Once the comments have been addressed and the guideline is edited, it can be submitted for publication. It is common that the guidelines are published in the journal of the organization or society. CPGs can also be made available on the society Web sites and submitted into clearinghouses such as NGC.[15]

Algorithm Development

Once a CPG has been developed, it sometimes becomes clear that the recommendations should also be outlined in a process map or clinical algorithm. These types of process pathways can be used to graphically demonstrate the decision-making logic and sequence. Algorithms are helpful when a CPG will be impacting a practice community where there are multiple health care providers involved in caring for the same patient population. In addition to creating easy visual organization of the practice process, an algorithm allows for “yes” and “no” decision points, which can easily be defined as a data point for measurement. It is often these crossroads in clinical decision making that can be identified as the basic for metrics, which can then be measured for assessment of compliance with best practices. These metrics can then be used to support appropriate and rapid changes in a practice process to continually improve the quality of health care.

There are increasing initiatives to improve the quality of health care. One of the ways for health care providers and medical societies to achieve this is through the development of evidence-based CPGs. CPGs have the ability to improve individual patient care and clinical outcomes by disseminating best practices while maintaining provider autonomy.

QUALITY METRICS

Assessing the quality of care focuses on three dimensions of care defined by Donabedian: structure, process, and outcome.[20] Structure is defined by the characteristics of a health system, such as a community hospital or a tertiary academic center. Process encompasses the activities performed by a health care provider. Outcome refers to results of the treatment affecting the patient, ranging from effects on quality of life to overall survival. In considering these aspects of care, it is frequently easier to measure process than outcome for assessing quality of cancer care, because a large number of factors, including comorbidities and patient preference, may influence patient outcome and may not be completely defined or measured.

The National Quality Forum (NQF) was established in 1999 as an expert panel and clearinghouse to distribute quality measures. There are currently 70 measures endorsed by the NQF relating to cancer.[21] For example, one measure documents the percentage of final procedure reports using fluoroscopy that document radiation exposure or exposure time. Another measure relates to overutilization of imaging studies in melanoma patients. None of these measures are directly related to cancer of the head and neck.

Measuring the quality of care for patients with cancer serves a number of important functions. Stakeholders, including patients, payers, and physicians, use the results to make informed decisions regarding treatment. Patients may decide among care centers or hospitals depending upon available quality measures or “grades.” Additionally, measuring quality of care can improve patient care. A cancer center or a specific department can evaluate its processes of care and determine rates of compliance with established standards (CPGs or NCCN head and neck cancer treatment guidelines). For example, patients with cancer of the head and neck with advanced cancer (T) stage or metastatic lymph nodes should be referred to radiation oncology for consideration of postoperative radiation therapy. Understanding levels of adherence to these guidelines and working to improve compliance should serve to improve patient care overall. Finally, measuring the quality of cancer care is critical for policy formulation. For example, routine preoperative imaging with a specific imaging modality may or may not affect treatment or improve outcome. Assessing the specific value of a preoperative imaging tool allows for decisions to be made at a system-wide level for such studies.

Establishing metrics that define quality care enables changes in the quality improvement process. The Shewhart cycle (Fig. 7.1), named for the quality engineer Walter Shewhart, has been used for several decades for industrial quality improvement and has more recently been used in the health care sector.[22] The premise of the cycle is continuous quality improvement, with the final step being ongoing monitoring to ensure the gains are held, and the ultimate goal of optimization of care is achieved.

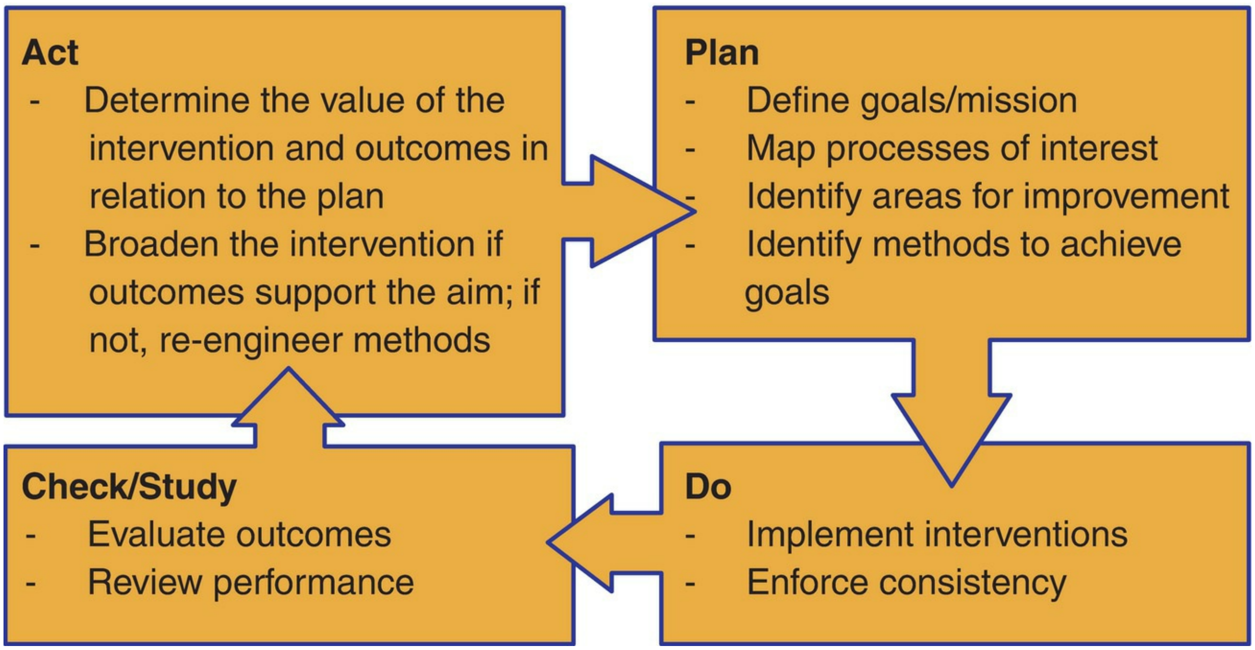

Figure 7.1. The Shewhart cycle.

Development of Quality Metrics

The establishment of quality measures typically evolves from the consensus of an expert multidisciplinary panel convened to review the literature and provide commentary; strong expert consensus is essential. A thorough and comprehensive review of the literature is performed to identify the available evidence regarding a particular process of care. This evidence is vetted to determine the level of evidence of the available clinical research (Table 7.1). The best process measure comes from research that a specific practice results in improved outcome(s). For example, patients treated surgically for squamous cell carcinoma of the head and neck with extracapsular extension of cancer detected in their cervical lymph nodes have improved locoregional control from the administration of postoperative adjuvant chemoradiotherapy

rather than radiation therapy alone.[23] In accounting for patient preferences, a quality measure may assess whether a treatment was offered or recommended rather than whether the treatment was actually performed. Once a quality measure is accepted, performance of physicians and/or institutions can be evaluated by adherence to this measure.

Table 7.1 Definitions of Levels of Evidence for Clinical Studies

Level	Study Type
1	a. Systematic reviews of randomized controlled trials
	b. Individual randomized controlled trials
	c. All or none studies
2	a. Systematic reviews of cohort studies
	b. Individual cohort studies
	c. Outcomes research/ecologic studies
3	a. Systematic review of case–control studies
	b. Individual case–control studies
4	Case series
5	Expert opinion

Adapted from Shin JJ, et al. Evidence-based medicine in otolaryngology, part 2: the current state of affairs. *Otolaryngol Head Neck Surg.* 2011;144:331–337, Reference 26.

Assessing outcomes of care is also essential in measuring quality of care. The IOM defines three general categories of outcomes: clinical status, functional status, and patient satisfaction. Clinical status relates to the biologic outcome of the disease, such as 5-year survival after cancer diagnosis. Other clinical outcomes include postoperative events, such as 7-day return to operating room, 30-day readmission rate, postoperative wound infections, or 30-day mortality rates. The assessment of functional status includes disease effects on the patient in the physical, emotional, and cognitive domains. Karnofsky performance status is a well-validated measure of patient functional status that also correlates with quality of life and predicts survival.[24] Patient satisfaction measures emotional attitudes of a patient toward his/her treatment. Although patients who are more satisfied are more likely to complete and follow through with treatment regimens, no correlation

exists between patient satisfaction and the quality of the care process.[25,27] Although important in understanding consumer attitudes, patient satisfaction may not be a useful measure of quality of care. Finally, a robust outcomes measure must account for factors that are not directly influenced by the health system. These variables include age, socioeconomic status, insurance status, race, cultural beliefs, and comorbidities. While measuring outcomes may seem most relevant to patient care, assessing quality of care requires outcome measures that can be directly attributed to a specific process of care.

Assessment of a health care provider focuses on adherence to quality measures. Administrative records can be examined, although they typically lack sufficient clinical detail; tumor staging is typically not part of the diagnosis code for insurance records. Medical records may be filled with clinical detail, but systematic reviews are labor intensive and not feasible at a national scale to evaluate patterns of care. Cancer registries were established by the National Cancer Act and may include information regarding tumor stage, first course of treatment, and overall survival. However, the level of detail can be quite variable and thus be inadequate as a data source to monitor cancer care quality. For example, although a cancer registry may capture pathologic assessment, postoperative chemotherapy and/or radiation therapy details may be lacking. Furthermore, the actual completion of recommended therapy is typically not present. The various limitations of these data sources clearly signal the need for a better reporting system.

Measuring Quality of Care in Head and Neck Surgery

The IOM recommended the development of a set of core quality measures to evaluate and monitor the quality of cancer care.[28] Treatment guidelines or CPGs are formulated from reviews of the existing literature and resultant multidisciplinary consensus recommendations. These guidelines enable individual physicians to deliver optimal evidence-based care for their patients. Adherence to some or all of these guidelines serves as the basis for measuring quality of care.

The AAO-HNS established the GDTF to write treatment guidelines. These guidelines serve to standardize care and decrease variation in care that can lead to poor quality of care. These guidelines are not in themselves quality performance measures and were not formulated for that purpose. Currently, available treatment guidelines cover general issues of

otolaryngology such as cerumen impaction and acute sinusitis.[29,30] To date, the AAO-HNS has not established guidelines for cancer of the head and neck.

As previously described, no cancer of the head and neck for specific performance measures are available in the NQF database. There are general performance measures that may be applied to care of patients with cancer of the head and neck. For example, there are metrics for systematic and complete pathology reporting that include tumor staging and histologic grade. The NCCN has developed treatment guidelines for cancer of the head and neck in a multidisciplinary format.[31]

AHNS established its Quality of Care Committee in 2007. The mission of this committee was to formulate evidence-based quality of care measures for patients with cancer of the head and neck. The committee was also charged to promote compliance with these standards as a framework to measure quality of care in head and neck surgery. A multidisciplinary committee was formed and began to develop quality measures in 2006. Working groups focused on metrics related to pretreatment, treatment, and posttreatment care. From the group recommendations, the entire committee approved two to four measures for each phase of care. The initial set of quality measures, which focused on cancer of the oral cavity, were approved by the Executive Council of the AHNS[32] (Table 7.2). The committee subsequently developed quality measures for cancer of the larynx, which were also then approved by the Executive Council of the AHNS[33] (Table 7.3). Assessment of adherence to these measures for the two most common head and neck cancers may serve as an important beginning for performance metrics in head and neck surgery.

Table 7.2 AHNS Quality Measures for Oral Cavity Cancer

Pretreatment measures:

1. All oral tongue cancer patients require documentation of pathology using College of American Pathologists criteria with histopathologic confirmation of disease.
2. All oral tongue cancer patients require documentation of the appropriate TNM staging (as defined by the American Joint Committee on Cancer).
   a. Assessment of primary tumor size (T)
   b. Assessment of regional nodal basins for metastatic lymphadenopathy (N)
   c. Assessment for systemic disease (M)
   This should include documentation of a complete head and neck examination, appropriate radiologic imaging of the head and neck, and chest x-ray.
3. Tobacco cessation counseling

Treatment-related measures:

1. All oral cavity cancer patients with advanced T stage or metastatic lymph nodes should be referred to radiation oncology for consideration of postoperative radiotherapy.
2. All oral cavity cancer patients with positive pathologic margins or metastatic lymph nodes showing extracapsular extension should be referred to a medical oncologist and radiation oncologist for consideration for adjuvant chemotherapy and radiation.

Posttreatment measures:

1. All patients treated for oral cavity cancer should have follow-up visits for symptom management and surveillance for recurrence and second primary tumors.
2. Patients treated with radiation therapy to the neck should have assessment of serum thyroid-stimulating hormone level to detect hypothyroidism. Posttreatment serum thyroid-stimulating hormone levels should be checked within 12 mo of completing radiotherapy.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Head and Neck Cancers. *Guidelines for Treatment of Cancer by Site*. 2009, Reference 31.

Table 7.3 AHNS Quality Measures for Laryngeal Cancer

Pretreatment measures:

1. All laryngeal cancer patients require documentation of pathology using College of American Pathologists criteria with histopathologic confirmation of disease.
2. All laryngeal cancer patients require documentation of the appropriate TNM staging (as defined by the American Joint Committee on Cancer).
   a. Assessment of primary tumor size (T)
   b. Assessment of regional nodal basins for metastatic lymphadenopathy (N)
   c. Assessment for systemic disease (M)
3. Tobacco cessation counseling
4. Prelaryngectomy counseling for patients undergoing laryngectomy

Treatment-related measures:

1. All laryngeal cancer patients with advanced T stage or metastatic lymph nodes should be referred to radiation oncology for consideration of postoperative radiotherapy.
2. All postoperative laryngeal cancer patients with more than one positive lymph node and/or advanced T stage should be referred to radiation oncology for consideration of radiation therapy.
3. All laryngeal cancer patients with positive pathologic margins or metastatic lymph nodes showing extracapsular extension should be referred to a medical oncologist and radiation oncologist for consideration for adjuvant chemotherapy and radiation.
4. All patients who undergo laryngeal surgery (partial or total) should be evaluated and followed by a speech pathologist.

Posttreatment measures:

1. All patients treated for laryngeal cancer should have follow-up visits for symptom management and surveillance for recurrence and second primary tumors.
2. Patients treated with radiation therapy to the neck should have assessment of serum thyroid-stimulating hormone level to detect hypothyroidism. Posttreatment serum thyroid-stimulating hormone levels should be checked within 12 mo of completing radiotherapy.

The development of quality of care measures for oral cavity cancer. *Arch Otolaryngol Head Neck Surg*. 2008;134(6):672, Reference 32.

Significant opportunities exist in cancer of the head and neck to improve quality of care. Two studies by Chen et al. report that treatment for cancer of the head and neck is more likely to reflect treatment guidelines at tertiary care centers.[34,35] Mortality rates are higher for patients with advanced cancer of the larynx receiving care outside teaching/research hospitals.[36] Patients with early-stage cancer of the larynx may also have a higher risk for death if treated at low-volume facilities.[37] Hessel et al. used 4 main quality measures and 26 clinical endpoints based upon institutional and NCCN guidelines to evaluate the care delivered to patients with cancer of the oral cavity in a tertiary academic department.[38] Lewis et al. employed NCCN guidelines as a quality standard to evaluate care for patients with cancer of the head and neck with recurrent or persistent disease referred to a tertiary care department.[39] These studies were able to use CPGs to define specific quality metrics and set a quality standard.

PERFORMANCE METRICS IN HEAD AND NECK CANCER CARE

The concept of measuring physician performance through outcomes reporting dates back to 1908, when Dr. Ernest Codman advocated that physicians review and try to improve their own patient outcomes.[40] He was later responsible for the development of the American College of Surgeons' (ACS) Hospital Standardization Program and the ACS Minimum Standards for Hospitals, published in 1917. In 1918, only 89 of 692 hospitals surveyed met these minimum standards.[40] The program continued to grow, eventually forming the basis for the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

Recent legislation has mandated institutional reporting of outcomes centered on specific medical conditions. Although the list of conditions does not currently include cancer of the head and neck, many outcomes are generalizable to our patients' care. There are currently multiple programs focusing on performance and outcome measurement at institutional, subspecialty, and even individual levels. We are currently positioned to develop standardized performance and quality metrics for head and neck cancer care, which may shape the future of our specialty.

Institutional Programs

There are currently many programs that serve to evaluate the quality of care delivered by a medical center as compared to national, risk-adjusted standards. The algorithms for risk adjustment, however, are unique to each program.[41] Many of these programs require an investment by the institution of both personnel and infrastructure, in addition to program-related expenses. One such example is the University Health System Consortium (UHC), which collects administrative data on inpatient hospitalizations and, based on hospital discharge coding, provides risk-adjusted institutional outcomes.

Specific to surgical performance, the AHRQ has developed patient safety indicators (PSIs) that can be evaluated using administrative data and specific software that produces risk-adjusted outcomes focused on in-hospital postoperative and postprocedure complications. Because it relies on administrative data, this program can be applied to administrative databases to set national performance benchmarks for specific surgeries and procedures against which an institution can then measure its own performance. Fargen et al. used the Nationwide Inpatient Sample (NIS) database to evaluate the PSIs associated with procedural management of unruptured cerebral aneurysms to establish an acceptable national benchmark of adverse events for these procedures.[42]

The ACS' National Surgical Quality Improvement Program (NSQIP) abstracts data from patients' actual medical records, including follow-up phone calls to patients, instead of relying entirely on administrative data. Data are collected by specifically trained Surgical Clinical Reviewers (SCRs), whose work is periodically assessed for interrater reliability. Not every surgery is reviewed; cases are selected to provide a random but representative sample of a hospital's surgical caseload. This program also includes a 30-day postoperative time frame during which data on adverse events are collected. These data are then risk-adjusted against the national database and each participating institution receives a biannual report revealing how it compares nationally. This program originally started in the Veterans Affairs hospital system, and over the course of 10 years, decreased postoperative morbidity by 45% and postoperative mortality by 27% through quality improvement spurred by this audit and feedback mechanism.[43]

Using these programs for measuring quality of performance does,

however, take significant institutional investment. Recognizing the costs associated with performance measurement programs, Keller et al. developed a scoring system to assess the quality of an institution's colorectal surgery performance based on administrative data. Using a national inpatient database, the authors were able to validate that their scoring system reflects an institution's colorectal surgery complication rate, thereby providing a low-cost alternative to existing programs.[44]

Surgical Specialty Programs

Although the list of medical conditions subjected to mandatory reporting of outcomes does not cover most surgical specialties, specialty efforts to develop performance metrics, such as those of Keller et al. for colorectal surgery,[44] have increased with widespread recognition of the need for performance improvement efforts. The Society of Thoracic Surgeons (STS) established a database in 1989 with the purpose of improving the quality of care in thoracic surgery. Participation is voluntary and participants must purchase the appropriate software and input their own data, but this database provides a mechanism for thoracic surgeons to receive quarterly reports of their own risk-adjusted outcomes in comparison to national data; data are risk-adjusted in three separate areas (adult cardiac, general thoracic, and congenital heart surgery) to account for variability in the field.[45]

Specific to cancer of the head and neck, Weber et al. created a program to evaluate the performance of head and neck surgeons, which was applied within their academic department. They found that performance metrics were affected not only by patient comorbidity and procedure acuity but the individual surgeon as well.[46] A follow-up study to evaluate the impact of structured feedback on surgeon performance found significant improvements in length of stay and the prevalence of negative performance indicators.[47]

Another approach to building a mechanism for evaluating specialty-specific performance is to modify an existing platform. The first criterion is to select a program that is clinically relevant. When compared to AHRQ-PSIs for a select patient population at one institution, NSQIP identified more clinically relevant adverse events and was found to be a better measure of quality performance.[48] NSQIP has inherent flexibility and has previously been evaluated for development of a surgical subspecialty (hepatobiliary)

option.[49]

Specific to surgical oncology, Merkow et al. utilized the National Cancer Data Base (NCDB) to include cancer-specific variables in NSQIP to evaluate the impact on risk-adjusted hospital rankings. They found no significant difference in hospital rankings with the addition of these variables, indicating that the existing NSQIP risk-adjustment variables were sufficient.[50] However, Borja-Cacho et al. evaluated NSQIP's predictive ability for complications after major thoracic, abdominal, or pelvic oncologic resections. They found that NSQIP had low predictive ability, suggesting the need for additional disease- and surgery-specific variables to accommodate complex oncologic surgeries.[51]

The Department of Head and Neck Surgery at the University of Texas MD Anderson Cancer Center recently undertook efforts to create a head and neck surgery–specific version of NSQIP. Realizing from previous departmental performance assessments that the highest acuity procedures (i.e., those requiring plastic surgical reconstruction) were associated with a significantly higher rate of negative performance indicators,[46] a panel of head and neck and plastic surgeons was assembled to identify variables that would tailor the NSQIP platform to provide clinically relevant data on head and neck surgery patients. Because head and neck oncologic surgeries represented only a fraction of the total number of the institutions surgeries, a dedicated SCR was hired to sample these high-acuity cases with 100% capture. Although in its infancy, this project is now being expanded on a national level to increase its power as a mechanism for assessing the risk-adjusted performance of head and neck surgeons.

Morbidity and Mortality Database

Morbidity and mortality (M&M) conferences are an integral part of the education surgeons and trainees and usually occur on a departmental level. There are clearly practical lessons to be learned from the surgical and medical complications discussed in such a forum. However, several studies have noted significant deficits in accurate reporting of complications and even mortality to this forum.[52,53] Improving reporting and data collection for M&M conferences not only allows department members to discuss the entire spectrum of challenges related to patient care but also develops an accurate

database for longitudinal analysis. The data can be analyzed to understand the patterns of errors and adverse events that may occur within the clinical practice. This baseline information is critical to understand the current level of function for a given surgical department and serves as a basis for comparison to institutional and national metrics as they are developed. Even without extensive adjustments for patient factors, especially comorbidities, the pattern and rate of complications for an entire service and individual surgeons are valuable.

In an effort to improve M&M case reporting in our department, we began recording events at the time of recognition or occurrence rather than in a retrospective fashion. The primary reporting responsibility was shifted to the residents and fellows, rather than resting with the faculty, on a database located on a secure institutional network server. The determination of a true complication event was made by the department quality officer or through discussion in conference if any questions arose. The accuracy of the data could be compared to available institutional data, such as in-hospital mortality, return to the operating room within 7 days of primary surgery, and hospital readmission within 30 days of discharge.

At our institution, we noted that a 2-year reporting period had 330 events involving 258 patients over 4,659 surgical procedures.[54] The overall complication rate was 7.1%. We were able to categorize the various events that occurred, including hematologic/vascular (e.g., hemorrhage), wound related (e.g., infection/abscess), technical (e.g., chyle leak), and respiratory (e.g., pneumonia). We were able to compare our numbers for hospital readmission and return to the operating room for intervention. Our data collection process was confirmed by the institutional data, which were identical with regard to mortality, return to the operating room, and hospital readmission.

Active tracking of M&M cases provides a valuable practice-based system for clinical education and internal auditing of the quality of patient care. The continued acquisition and longitudinal analysis of this data provide a crucial internal benchmark for complications in order to make comparison against available data in the literature and with institutional and national metrics of quality of care at the individual surgeon and institutional level.

Individual Assessment

The work done by Weber et al. specifically addressed the performance of individual surgeons.[46] In the authors' follow-up study, performance was reevaluated after individual surgeons received their data as compared to anonymized departmental data and significant improvements were found (manuscript in preparation). The head and neck surgery version of NSQIP has also built in individual surgeon identification to allow for individual risk-adjusted feedback, much as the STS has done over the past 25 years.[45]

Although legislation in the United States has focused on institutional-level reporting, physicians realize the importance of individual performance assessment. Because of this, many performance improvement programs have their success rooted in physician feedback. In an effort to standardize blood transfusion indications in cardiac surgery patients, Beaty et al. performed an initial review of provider practices and then presented their providers with aggregate data, which was followed by an improvement in adherence to blood transfusion protocols. After this second audit, individual providers were then given individual feedback, which was followed by an additional improvement in adherence.[54] The importance of evaluating individual performance is highlighted in a study by Foglia et al. in which 5 (7%) surgeons were found to be responsible for 29% of surgical delays and 4 (8%) anesthesiologists were found to be responsible for 45% of anesthesiology delays,[56] having individual assessment allowed for more targeted performance improvement that decreased operating room delays institutionally.

A recent observational study highlighted the many reservations that physicians have about more public reporting of individual performance metrics. Although most of the surgeons interviewed indicated that they believed such measures would lead to quality and performance improvement, they raised concerns about data validity based on small sample size and coding accuracy, as well as about outside consequences, including misinterpretation of data by others and surgeon refusal to treat high-risk patients in order to better their performance.[57] These sentiments echo concerns about the recent public reporting of individual surgeons' outcomes by the National Health Service in the United Kingdom.[58] Although physician performance is important to assess in order to effect improvement in the quality of the care we provide, consideration must be given to how these data are collected and risk-adjusted and with whom and in what context they are

shared; these are issues that remain to be addressed as we move forward with performance improvement and reporting in head and neck cancer care.

CONCLUSION

Quality improvement is integral to conserving resources and ensuring the best possible care. Knowledge of measurable outcomes and the impact of delivered care on these outcomes should serve as an impetus for improving care through the identification of best practices.

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8 Nonmelanoma Skin Cancer

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Nonmelanoma skin cancer (NMSC) is the most common malignancy worldwide and is managed by a diverse group of clinicians, including primary care physicians, dermatologists, otolaryngology—head and neck surgeons, surgical oncologists, plastic and reconstructive surgeons, and radiation oncologists. It is important that treating clinicians have a clear understanding of the epidemiology, staging, management, and prognosis of this disease. NMSC is a heterogeneous group of malignancies encompassing many different histologic subtypes, requiring different management approaches, and with widely varying prognoses.[1] These malignancies range from ubiquitous lesions, such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), to relatively uncommon lesions, including Merkel cell carcinoma (MCC), adnexal carcinomas, and mesenchymal tumors, such as cutaneous angiosarcoma and Kaposi sarcoma (KS).

EPIDEMIOLOGY

The most common NMSC is BCC, which constitutes 70% to 75% of cases, followed by SCC (20% to 25%).[2] MCC constitutes <5% of NMSC, and other histologic subtypes make up the remainder.[3,4] In general, males are affected more often than females, and the incidence increases with age.

The prevalence of NMSC has reached epidemic rates in regions such as Australia, where the incidence of skin cancer is the highest in the world.[2] Worldwide, there are differing rates of NMSC in various populations, but in most regions, the incidence is increasing.[2,5,6]

In Australia, the incidence of NMSC has risen significantly from 1985 to 2002, with the annual incidence of BCC increasing from 657/100,000 to 884/100,000, and SCC more than doubling from 166/100,000 to 387/100,000.[2] This continued increase has occurred despite recent public health campaigns, such as “SunSmart,” which advocates protective clothing, sun protection factor in excess of 30+ sunscreen, and avoidance of excessive sunlight, especially during peak sunlight hours.[7] In 2002, the incidence of NMSC in Australia was more than 5 times that of all other cancers, combined with an annual rate of 1,170/100,000.[2] In the United States, over 1 million new cases of NMSC are diagnosed annually.[8]

Death from NMSC is low compared with other cancers. Between 1998 and 2005, there was an average of 382 deaths per year in Australia, ~1 to 3 per 100,000.[9] Overall, NMSC has a good prognosis, with a low recurrence rate and >90% 5-year disease-specific survival rates. Despite this, NMSC, and in particular a subset of patients with high-risk SCC, can still provide a challenge for both patient and clinician, due to the development of locally recurrent disease in ~10% and the propensity for metastasis to the neck in 3% to 5% of patients.[10–13] Patients diagnosed with either an SCC or an MCC are at risk of developing metastasis and dying of their disease. Death resulting from BCC is extremely rare.

ETIOLOGY

Ultraviolet Radiation

Environmental exposure to ultraviolet (UV) radiation is the major etiologic factor that damages DNA and leads to the development of NMSC. The pathogenesis of SCC strongly correlates with cumulative exposure of UV radiation, in particular, UVB (290 to 320 nm). The sun-exposed head and neck is the region of the body most frequently affected by NMSC.[3] Risk factors include increasing age (particularly age over 70 years[2]) male gender, Caucasian ethnicity, chronic sun exposure, outdoor occupation, acquired or inherited immunosuppression, and certain rare systemic diseases such as epidermolysis bullosa, oculocutaneous albinism, and xeroderma pigmentosum (XP).[1,14–16] Additional factors such as proximity to the equator, ozone layer depletion, and both occupational and recreational

exposure significantly increase this risk.[15] NMSC is rare in dark-skinned races due to the protective role of melanin in UV-induced damage of skin cells.[17]

Immunosuppression

Immunosuppression such as in solid organ transplantation, hematologic malignancies, including non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL) (Fig. 8.1) and human immunodeficiency virus (HIV) infection increases the risk of NMSC. Posttransplantation patients and those with autoimmune disorders, or on immunosuppressive agents, exhibit an increased risk, particularly of SCC, with increasing risk associated with increasing duration of immunosuppression.[18,19] Recipients of solid organ transplants exhibit approximately a 100-fold increase in the risk of developing SCC compared with a 10- to16-fold increase in risk of developing BCC.[20] The risk for developing cervical lymph node metastases lies between 10% and 18%,[21,22] and the risk of death is significantly increased in patients who develop SCC after a renal transplant.[23]

Figure 8.1. Elderly male suffering from chronic lymphocytic leukemia

(CLL) presenting with a rapidly enlarging scalp SCC with concomitant metastatic lymph nodes in his ipsilateral posterior neck, as well as nodes enlarged secondary to CLL. Such aggressive behavior is rarely witnessed in nonimmunosuppressed patients.

Treatment-related immunosuppression, which classically occurs in solid organ transplant recipients, results in an 18 to 250 times increased risk of SCC[24,25] and, to a lesser extent, BCC. Furthermore, there is a greater risk of developing metastasis involving both regional and distant sites.[26] In the Australian transplant population, at least 45% of patients developed an SCC within 10 years of transplantation, whereas patients from Europe had an incidence of 10% to 15% at 10 years following transplant.[27] In the renal transplant population in Queensland, Australia, the incidence of NMSC at 20 years was 81%, with 75% having invasive SCC.[28]

Immunosuppression secondary to HIV has a different effect on NMSC. Associated with this greater incidence is a propensity for aggressive SCC, and an increased rate of spread to regional lymph nodes. Unlike other forms of immunosuppression, there does not appear to be an alteration in the ratio of BCC to SCC. Currently, it is unclear if CD4 count or HIV viral load affects the development of NMSC in HIV patients.[29] There are current data to support a role for human papillomavirus (HPV) in the development of SCC. This association has been demonstrated in the immunocompromised population, where up to 90% of tumors contain HPV DNA.[30]

Gene Mutations and Inherited Conditions

As with all malignancies, acquired and inherited mutations are involved in the pathogenesis of NMSC. The p53 tumor suppressor gene has an important regulatory role in the cell cycle, as well as in DNA repair and apoptosis.[31] Mutations of this gene are implicated in the etiology of many cancers, including SCC and BCC. Alterations in pyrimidine dimers, induced by UV radiation, may inactivate this gene, causing dysregulation of the cell cycle, failure of apoptosis, and tumor formation.[32] Another gene relevant in the pathogenesis of BCC is patched (*PTCH1*), located on chromosome 9, which was first identified in individuals with the autosomal dominant BCC nevus (Gorlin) syndrome.[33] Patients with this syndrome have defects in the sonic

hedgehog signaling pathway and present with multiple BCCs, odontogenic cysts, skeletal defects, palmar and plantar pits, and calcification of the falx cerebri.[33]

Other inherited conditions, including the autosomal recessive XP, can predispose individuals to a 100-fold increase in the risk of NMSC. In this condition, cells have an impaired ability to repair UV-induced damage, leading to multiple SCC and other skin cancers. The mutation involved disrupts the nucleotide excision repair, which enzymatically repairs UV-induced DNA damage.[31] Epidermodysplasia verruciformis is another autosomal recessive condition, in which increased susceptibility to viral oncogenesis, secondary to HPV infection, results in widespread wart formation followed by the appearance of cutaneous SCC.[34]

Cigarette Smoking and Carcinogens

Cigarette smoking has been implicated in the development of many malignancies, although its role in the development of NMSC is controversial. A Dutch study showed a doubling of the risk of development of cutaneous SCC in smokers with an associated dose response.[35] Some studies have supported the association, quoting increased rates of 1.5 to 4 times, whereas other studies have found no association. In contrast to the Dutch study, a large prospective study involving over 300,000 construction workers in Sweden did not find any association between smoking and the development of SCC.[36]

Other risk factors include exposure to chemical carcinogens, such as arsenic.[37] Arsenic is associated strongly with the development of a variety of dermatologic manifestations and malignancies, including SCC and BCC. Areas of chronic irritation and scarring also predispose to SCC, which is known to arise in chronic “Marjolin” ulcers, sinus tracts, and scars.[33]

Precursor Lesions

Actinic keratosis (AK) is a dysplastic keratinocytic lesion arising within the epidermal layer of the skin, induced by UV radiation.[14,38] In Australia, up to 50% of people over 40 years of age have one or more AK.[14] Although a substantial proportion (25% to 75%) of AK regress over time, a number

eventually progress to invasive SCC. Estimates of the rate of progression of an individual AK to SCC have been reported at up to 20%. Despite this, two longitudinal studies have reported a considerably lower annual rate of transformation—0.096% per year[14]; and 0.60% at 1 year and 2.57% at 4 years.[38] These studies reported that 60% to 65% of SCC arose from preexisting AK. Although the chance of an individual AK transforming into invasive SCC is low, individuals at risk usually have multiple AK, with one study documenting an average of 46.

BASAL CELL CARCINOMA

Clinical Presentation

Unlike SCC, BCC arises *de novo*, with no obvious precursor lesions. The nodular subtype is the most common and accounts for ~60% of BCC. Other variants are superficial or infiltrative. Nodular and morpheaform are the most common subtypes in the head and neck region; superficial BCCs commonly occur on the trunk.[39]

Nodular BCC typically presents as a “pearly” telangiectatic nodule with rolled borders. Central ulceration, crusting, and bleeding may occur. Superficial BCC may present as an asymptomatic plaque or papule and is pink/red in color. Most are asymptomatic, with ulceration, itching, and bleeding being uncommon. Morphoeic lesions are smooth, flesh-colored plaques or papules resembling scars with ill-defined borders.[40] They are often long-standing asymptomatic lesions and may be deeply invasive by the time of diagnosis. Perineural invasion (PNI) is frequently present. In the head and neck, the nose is the site most commonly affected, followed by other sun-exposed areas, such as the scalp and ear.[41,42] Prospectively acquired data in Australia have shown that 57% (379 out of 663) of BCCs were located in the head and neck, with the nose, cheek, forehead, and ears most commonly affected.[43] BCC rarely spreads to involve regional lymph nodes.

Histology

BCC is typified by collections of cells resembling the basal layer of the epithelium. Retraction between the stroma and tumor may be present as an

artifact and helps to differentiate BCC from appendageal tumors of similar appearance.[44] Morphoeic BCC differs histologically from the other subtypes of BCC as the stroma contains little mucin and retraction artifact is rare. PNI does occur but is uncommon.

Management

A punch or incisional biopsy of the lesion is required for initial diagnosis. As BCCs rarely metastasize, staging investigations are unnecessary, but computed tomography (CT) scans of the head and/or neck are performed in cases of locally advanced cancer to assess depth of invasion and involvement of functionally important soft tissue and bony structures (i.e., parotid gland (PG), external auditory canal, petrous temporal bone).

Surgical

Lesions are excised, typically with a margin of 3 to 5 mm. The majority of lesions can be excised and closed primarily. In patients in whom primary closure is not feasible, local flaps and skin grafts are used (Fig. 8.2). A positive margin has been reported to be associated with a 30% to 40% local recurrence rate,[45] and in these cases, patients should be considered for further surgery or adjuvant radiotherapy (RT). Positive margins underlying local flaps should rarely be left untreated because of the risk of undetected and delayed deep recurrence. Selected patients, such as those with morphoeic or recurrent BCC, can be referred for Mohs micrographic surgery, a technique in which serial sections of skin are excised and the peripheral and deep margins examined, so that 100% of the surgical margins are evaluated. Patients with morphoeic and large BCCs require wider surgical margins to maximize the chance of complete resection. For primary morphoeic lesions, the rate of complete excision with increasing peripheral surgical margins is 3-mm margin, 66%; 5-mm margin, 82%; 13- to 15-mm margin >95%.[46]

Figure 8.2. A 65-year-old female having undergone excision and grafting of a lower dorsum BCC. Midface lesions that require reconstruction, especially of the nose, may not always achieve an optimal cosmetic outcome.

Nonsurgical

A variety of nonsurgical options are also available to the clinician, including RT, cryosurgery, photodynamic therapy, curettage and cautery, topical

treatment, and intralesional injection.

Only a few randomized controlled trials have reported on the outcome of RT on patients with BCC. A Cochrane review suggested that either RT or surgery results in the lowest recurrence rates.[47] A trial of 347 patients examining RT versus excision of facial BCCs of <40 mm in diameter demonstrated fewer recurrences in the surgical cohort at 4 years (RR 0.09), and that cosmetic outcome was enhanced postsurgery (87% rated as “good”) at 4 years compared with RT (69%).[48] Conversely, in a separate trial of 374 patients, no significant difference was seen in recurrence rates between patients receiving RT or Mohs surgery, and overall cosmetic outcome did not differ between treatment groups.[49] RT is an effective option if surgery is declined or the outcome (form and/or function) is likely to be better nonsurgically.

Adjuvant RT is an option in the setting of close or positive excision margins, especially if a flap has been used for reconstruction, as detecting deep recurrence, especially in the midface, can be difficult. Up to 30% of incompletely excised BCCs will recur locally,[50] making RT a useful modality, especially if reexcision is not an option. In a trial of adjuvant RT versus surgery alone, RT improved the 5-year local control rate from 61% to 91%.[51] Ten-year local control rates were similar between the two groups (92% vs. 90%), indicating that most local recurrences can be salvaged surgically, although some patients require reconstruction after wide local excision. Patients with infiltrative BCC, particularly those with PNI, should be considered for adjuvant RT, given the propensity of these tumors to recur locally or spread to the skull base through perineural pathways.

Patients with XP should not undergo RT especially at a younger age because of the risk of inducing skin cancers. Similarly, lower limb lesions, especially in older patients suffering from diabetes and peripheral vascular disease, should not be irradiated if possible, because of the risk of delayed wound healing.[52]

SQUAMOUS CELL CARCINOMA

Clinical Presentation

Morphologically, the appearance of SCC exhibits a range of phenotypic variation. Classically, the appearance is of a shallow ulcer with raised, indistinct borders. A plaque often covers the lesion. Similar to BCC, sun-exposed areas of the head and neck are most commonly affected, with involvement of the lip or ear associated with a poorer prognosis and increased risk of metastases. Local symptoms and signs, such as numbness, pain, trismus, tumor immobility, paresthesias, dysesthesias, and cranial nerve palsy, are signs of advanced disease and may indicate deep tissue invasion and/or underlying perineural spread, which are poor prognostic factors.[16]

Patients with SCC may have a history of premalignant lesions, most commonly AK. Invasive SCC may also occur in the absence of a history of premalignant lesions. Bowen disease (intraepithelial SCC) presents as well-demarcated, erythematous, scaly keratotic papules and plaques.[53] The presence of nodal metastases has a potential adverse impact on prognosis in terms of morbidity, mortality, and quality of life.[54] Distant spread is rare but may occur in more advanced, neglected, and/or recurrent cancers. Lung and bone are reported to be the most common sites of distant metastasis,[55,56] with the liver and brain also potentially affected.[16] In a study of 122 patients treated for metastatic SCC, 7% developed distant metastatic disease, with the lung the most common site.[56]

Histology

SCC and its precursor lesions (AK and Bowen disease) are characterized by sheets and ridges of squamous cells. AK involves only part of the epidermis, Bowen disease involves the full thickness of the epidermis, and invasive SCC spreads beyond the basement membrane. SCC arises from the keratinocytes of the spinous layer of the epidermis. There is infiltration of the dermis by atypical squamous cells surrounded by an inflammatory infiltrate. The degree of cellular differentiation is categorized as mild, moderate, or severe and is of prognostic value. The degree of differentiation correlates with the extent of keratinization, nuclear hyperchromasia, and increased mitotic activity.[44] The more poorly differentiated the tumor, the fewer keratin pearls are present. The depth of anatomic invasion is indicated by Clark's level staging system[57]:

- Level 1: SCC confined to the epidermis (SCC *in situ*)

- Level 2: Invasion into the papillary dermis
- Level 3: Invasion to the junction of the papillary and reticular dermis
- Level 4: Invasion into the reticular dermis
- Level 5: Invasion into the subcutaneous adipose tissue

Metastasis to the Neck

The risk of developing lymph node metastasis in patients with SCC is uncommon, and ~3% to 5%, but increases in patients with unfavorable primary tumor features, that is, high-risk SCC.[11–13] Patients developing local recurrence are at higher risk of lymph node metastasis.[10,12,58] The parotid gland (PG) is the most frequent site for metastasis in patients with head and neck primaries. Patient factors that predict the development of metastasis include male gender, immunosuppression, and delayed presentation.[11,59] Tumor factors include histologic grade (poorly differentiated or undifferentiated), size (>2 cm), depth/thickness (>4 mm), invasion of adjacent tissue, anatomic location (ear, lower lip, and cheek), presence of perineural and/or lymphovascular invasion (LVI), and growth rate. Over 70% of lymph node metastasis presents within 1 year of treatment of the primary lesion, whereas few patients present with lymph node metastasis after 5 years.[12]

Regional nodes can be separated broadly into two groups, namely, parotid (preauricular and parotid tail) and cervical nodes (levels I to V). The location of a primary cutaneous SCC is an important determinant of the site of potential lymph node metastasis. The most frequent location for such a lesion is the lateral aspect of the head (Fig. 8.3). Metastasis is most commonly identified in parotid, level II (i.e., jugulodigastric), and external jugular chain nodes. Parotid nodes represent the first echelon of lymphatic drainage from the face, forehead, anterior scalp, temple, and ear. In Australia, metastatic cutaneous SCC is the most common malignant neoplasm of the parotid.[60] Facial lesions tend to metastasize to level I and II cervical nodes, whereas anterior lesions of the scalp, ear, temple, and forehead usually metastasize to parotid +/− level II cervical lymph nodes.[61] Drainage to multiple first echelon nodes is common. Drainage to contralateral nodes occurs in 10% of patients, predominantly in those with midline cancers.[62] Cancers posterior to the tragus usually metastasize to level V or the occipital nodes.

Figure 8.3. A 62-year-old bedbound, poor performance patient with a 3-cm thick poorly differentiated SCC located in his left preauricular region. Clinically, he was node negative but considered at risk of harboring occult nodal metastases. Being medically inoperable, he proceeded to wide-field high-dose radiotherapy (50 Gy in 20 fractions). Note the generous radiotherapy field (as marked) to treat potential subclinical spread.

High-Risk Tumor Features

Tumor size, using a cutoff of 2 cm (Fig. 8.4), is associated with a significant difference in the rate of lymph node metastasis.[10,11,63] There is, however, a limitation in applying two-dimensional tumor size as a sole prognostic factor. In a study of 266 patients with metastatic lymph node metastasis, where 70% of lesions were <2 cm in size, tumor thickness was >4 mm in the majority of patients with T1 lesions, all of whom had metastasis.[58] There was a significant correlation between increasing thickness of the cancer and size of the lesion, suggesting that these cancers had a propensity for both vertical and

horizontal growth. It was noted that not all large SCC metastasized, inferring that lesions that are horizontally large (2 to 3 cm), but not thick (i.e., 2 to 3 mm), may lack the tendency to metastasize.

Figure 8.4. An 82-year-old male who 9 months previously underwent excision of a 12-mm SCC. He now presents with biopsy-proven metastatic nodal SCC to his ipsilateral preauricular lymph nodes. The lateral forehead and temple should be considered as high-risk anatomic locations as the lymphatic vessels drain to the nearby parotid and upper neck.

Thickness of the cancer is also of prognostic importance.[12] Thickness of the cancer >6 mm was a highly significant independent predictor for the development of metastases in a large German prospective study.[12] Fourteen of 90 patients with cancers thicker than 6 mm developed regional metastasis, whereas no patients with cancers thinner than 2 mm developed regional metastasis. Another study demonstrated that although only one-third of patients with SCC have lesions >4 mm thick, these accounted for >80% of cancers developing metastatic nodal disease.[22] In a study involving more than 500 patients, no patients with an SCC of thickness <2 mm developed metastasis, whereas approximately 20% of patients with a lesion >5 mm developed regional nodal metastases.[64] In keeping with thickness, Clark levels have also been investigated and reported to be predictive. SCC measuring <4 mm thick or Clark level I to III had a metastatic rate of 6.7%, whereas the rate for SCC > 4 mm thick or Clark level IV or V was 45.7%.[10]

Desmoplastic SCC is an aggressive histologic variant, most frequently found on the ears, nose, and forehead. It is characterized by the presence of PNI, an invasive clinical course, and poor prognosis.[65] Patients with desmoplastic SCC have 10 times the risk of local recurrence and 6 times the risk of metastasis compared with other SCC subtypes.[64] Desmoplasia is reported to be the most important histologic feature for local recurrence, with 24% of 51 patients with desmoplasia versus 1% of 564 patients without desmoplasia developing local recurrence.[12]

Recurrent cancers are associated with a marked increase in the risk of developing metastases to the neck. Patients with inadequately excised SCC are at risk of both local recurrence and the development of nodal metastasis. The risk of nodal metastasis has been shown to be 15% in patients with recurrent lip SCC, compared with 2% in those with *de novo* lesions.[10] The incidence of lymph node metastasis was 32% and 45% in the setting of recurrent lip and ear SCC, respectively.[58] In one study, 18% of 78 patients had metastatic cancer following tumor recurrence (HR 2.81).[66] In a review of 122 patients with metastatic SCC, 11% of patients had lesions that were recurrent.[56]

Poorly differentiated SCC is more likely to be associated with the development of regional metastases. A significant difference in the rate of nodal metastasis between high- and low-grade SCCs (17% vs. 4%) has been

reported.[67] Other studies have demonstrated a difference in tumor behavior, based on histologic grade, with the rate of poorly differentiated SCC increased in patients developing metastasis (44% vs. 5%).[63] An Australian study also supported this finding, with 46% of patients with nodal metastasis displaying moderate or poor differentiation of their primary SCC, compared with 12% with a well-differentiated grade.[58]

Perineural invasion (PNI) refers to tumor growth in or around a nerve[68] and occurs by the contiguous spread of malignant cells along the potential space between a nerve and its surrounding sheath. PNI occurs in <5% of all cutaneous malignancies and is more common among SCC, involving 2.5% to 14% of cases, compared with 0.18% to 10% of BCC.[69] The presence of PNI is significant in that it confers an increased risk of recurrence in both BCC and SCC and the development of metastasis in SCC, and a poorer prognosis due to more aggressive tumor behavior.[69] The risk of death from PNI is much less likely with BCC.

PNI can be broadly classified as either "incidental" or "clinical." Incidental PNI is identified only at histopathology in clinically asymptomatic patients with negative imaging. Other terms used in the literature to describe incidental PNI include "minimal" or "microscopic" PNI. PNI is classified as "clinical" when the patient exhibits sensory or motor changes or there is radiographic evidence of perineural spread within a named nerve. It may also be referred to as "extensive" or "macroscopic" PNI.

The distinction between incidental and clinical PNI is prognostic. One study reported a 5-year local control rate of 80% for cutaneous malignancies with incidental PNI, compared with 54% for clinical PNI, despite aggressive treatment with RT +/− surgery and/or chemotherapy.[70]

A study on PNI in SCC demonstrated that the presence of additional tumor-related high-risk factors was associated with poorer outcomes, and concluded that these patients should also be considered for adjuvant RT.[71] Factors identified included poor differentiation, tumor diameter ≥2 cm, and invasion beyond subcutaneous adipose tissue. Significantly, patients with involvement of large nerves (≥0.1 mm) were also found to be more likely to have such concomitant adverse features.

The main challenge in managing patients with clinical PNI is achieving durable control of their disease. Appropriate resection with margin control

plus adjuvant RT is likely to offer select SCC patients with clinical PNI the best chance of cure. Even tumors previously considered potentially unresectable, such as those with extensive intracranial PNI involving cranial nerves up to the gasserian ganglion (zone 2), may be operable, and this treatment potentially offers improved survival with acceptable morbidity.[72]

High-dose definitive RT alone can also offer the chance of cure in ~50% to 60% of suitable patients, but with associated acute and late side effects. Intensity-modulated (IM) RT offers the ability to treat accurately defined volumes considered at risk, or involved, and at the same time limit the RT delivered to important structures at risk, such as the visual pathways and brain. The fusing of diagnostic magnetic resonance imaging (MRI) scans with RT simulation scans allows improved determination of the target volume.[73]

Lymphovascular invasion (LVI) denotes invasion of tumor cells into the microvasculature of the dermis and lodgment within a vessel lumen and has been demonstrated to be an independent risk factor for nodal disease (40% node positive vs. 8% node negative).[74] In a large study of 4,740 patients treated for SCC, multivariate analysis identified LVI as a significant risk factor for metastatic disease in patients with a lesion in the cheek or periauricular region (HR 3.18 and HR 3.31, respectively), but not at other sites of the head and neck.[75]

Anatomic subsites have been identified as being at increased risk for the development of nodal metastases. The most common primary sites leading to parotid and/or neck metastases, in descending order of frequency are the lip, cheek, ear, temple, forehead, scalp, and nose.[56,76,77] The most common primary sites leading to parotid metastases are temple/lateral forehead and preauricular area and cheek.

Positive excision margins are associated with recurrent SCC in up to 50% of patients (Fig. 8.5).[78] An excision margin of 6 mm in patients with high-risk SCC is recommended. In two studies, an excision margin of 4 to 5 mm for low-risk SCC resulted in tumor clearance in 95% to 97% of cases compared with 78% clearance when a 2-mm excision margin was applied.[79,80]

Figure 8.5. Recurrent SCC in a 92-year-old female. She previously underwent three excisions in the same site without being considered for adjuvant local radiotherapy, despite close and positive excision margins and recurrence. The extent of her recurrence precluded salvage surgery and has recommended wild-field radiotherapy (40 Gy in 10 fractions using orthovoltage photons) with protection of her globe. Her parotid and cervical lymph nodes will be clinically observed.

Staging

The 7th edition of the American Joint Committee on Cancer (7th AJCC) tumor, node, metastasis (TNM) staging system is widely used in staging the primary SCC and neck.[1] Previous editions of the AJCC TNM classification did not differentiate between subtypes of NMSC and were criticized for this. Previously, only the horizontal extent of the primary lesion was considered important when differentiating T stage, with nodal metastasis classified as either N0 or N1, to indicate presence or absence of regional involvement.[1]

The 7th AJCC staging system now incorporates multiple high-risk features when determining the T stage of an SCC and differentiates early lesions (T1 or T2) based on size (2 cm threshold) and the absence or presence of other tumor-related features such as thickness >2 mm, PNI, poor differentiation, and location on the ear or non–hair-bearing lip (Table 8.1). Advanced lesions (T3 and T4) are uncommon and based on the degree of local invasion into surrounding tissues. Of note, an obvious index lesion is not present in a minority of patients (20% to 30%) who present clinically with metastatic SCC of the head and neck, although most will have a past history of NMSC.[58]

Table 8.1 Staging for Cutaneous SCC (7th Edition of AJCC Staging Manual)

Tumor		Node		Metastasis	
Tx	Primary tumor cannot be assessed.	Nx	Regional lymph nodes cannot be assessed.	M0	No distant metastases
T0	No evidence of primary tumor	N0	No regional lymph node metastases	M1	Distant metastases
Tis	Carcinoma *in situ*	N1	Metastases in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
T1	Tumor <2 cm in greatest dimension with <2 high-risk features	N2a	Metastases in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		
T2	Tumor >2 cm in greatest dimension or any tumor with 2 or more high-risk features	N2b	Metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone	N2c	Metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base	N3	Metastases in a lymph node more than 6 cm in greatest dimension		

High-risk features: >2 cm in size, >2 mm thickness, or Clark level ≥ IV, presence of perineural invasion, located on the ear or non–hair-bearing lip, poorly differentiated, or undifferentiated.Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

O’Brien et al. (Table 8.2) recognized the significant limitation of the TNM system when proposing a new staging system, based on extent of metastatic regional disease involving the parotid and/or cervical neck nodes.[81] Eighty-seven patients who had been treated with curative intent for metastatic SCC of the head and neck were restaged according to this new

system, which separated nodal metastasis (size, number, and site) in the parotid (P) and neck (N). Multivariate analysis demonstrated that although increasing P stage, positive margins, and failure to have multimodality therapy were associated with increased risk of recurrence in the parotid, neither increased P stage nor type of therapy were significant for survival. However, both increasing N stage and positive margins were found to be predictive of worse disease-specific survival.

Table 8.2 O'Brien et al. System for Clinical Staging of Metastatic Cutaneous SCC Involving the Parotid Gland +/− Neck

Parotid		Neck	
P1	Metastatic node up to 3 cm diameter	N0	No clinical neck disease
P2	Metastatic node more than 3 cm up to 6 cm in diameter or multiple parotid nodes	N1	Single ipsilateral neck node up to 3 cm diameter
P3	Metastatic node more than 6 cm in diameter or cancer involving VII or contralateral nodes	N2	Single node more than 3 cm diameter or multiple neck nodes or contralateral nodes

Palme et al. subsequently tested this new P and N staging system on a separate group of patients from the Head and Neck Service, Westmead Hospital, Sydney.[82] One hundred and twenty-six patients with SCC metastasizing to the parotid and/or neck were retrospectively restaged. The results demonstrated that increasing P stage was associated with a reduction in local control and increased treatment failure within the parotid bed. Immunosuppression, single modality therapy, and increasing P stage were all found on multivariate analysis to be significantly associated with decreased survival. However, unlike the study of O'Brien et al., increasing N stage was

not found to be significant.[82]

A modification of the O'Brien staging system, including the parotid and remaining neck nodes, was introduced to include well-accepted nodal factors, such as size, location, and number, in order to improve prognostication and simplify staging of patients with metastatic SCC of the head and neck.[83] This proposed system was tested against a cohort of patients from the authors' institution and externally validated against a separate group from Westmead Hospital, Sydney. In both instances, the stratifications were found to have prognostic significance. The nodal classification in the N1S3 system is similar to that of the current 7th edition of the AJCC, which was modified based on results from published studies.[81]–[85]

Investigations

Following a thorough history and clinical examination of the primary cancer and head and neck region to ascertain the presence of nodal metastasis, and assessment of any neurologic deficit (cranial nerve palsy or sensory deficit) from PNI, histologic diagnosis of the primary is confirmed with an excisional biopsy for small lesions and punch or incisional for larger lesions. A fine needle aspiration of any palpably enlarged nodes should be undertaken under ultrasound guidance.

The majority of low-risk patients without palpable lymph nodes do not require further radiologic evaluation. The presence of high-risk clinical or histologic features—large or neglected tumors, recurrent disease, or suspected cranial nerve involvement, including the facial and/or trigeminal nerves, the immunocompromised host, or extracutaneous involvement—may indicate a need for further radiologic evaluation of the primary and local and distant metastatic disease.[86] A contrast-enhanced CT scan will assess the depth of invasion of the primary and whether underlying bone is involved. Central hypoechogenicity, round shape, and enlarged size of a lymph node are suggestive of metastatic disease. Loss of adjacent nodal adipose tissue planes indicates extracapsular spread. An MRI scan will provide information regarding infiltration of critical soft tissues, including orbit, brain, and, in particular, cranial nerves.

In a prospective study of 48 patients with head and neck cancer undergoing neck dissection, the modalities of palpation, ultrasound, and CT

findings were compared with the gold standard of histopathologic examination of lymph nodes.[87] Palpation had a positive predictive value and negative predictive value of 78% and 74%, respectively. In comparison, the corresponding values for ultrasound were 94% and 80%, and for CT 90% and 85%. However, similar data specific to cutaneous SCC are lacking.

Management

The optimal approach to a high-risk patient is surgery, preferably Mohs micrographic surgery.[88] However, this option is not always available, and alternatives include wide excision +/− adjuvant RT or definitive RT (Fig. 8.6A and B). The aim of surgery for a patient with SCC (low or high risk) is to obtain negative excision margins, which typically range from 3 to 10 mm, depending on patient and tumor variables. It is unacceptable to observe patients with inadequately excised SCC because of the risk associated with recurrence. Re-excision or adjuvant RT should be offered in this situation.


A

Figure 8.6. A: Deeply invasive SCC overlying the left parotid gland. The

planned excision margin is illustrated on the patient. **B:** Wide excision of the lesion down to the parotid fascia.

Definitive RT is an efficacious option for both low- and high-risk SCC,[89] and, as with BCC, attention needs to be paid to the cosmetic and functional outcomes of surgery versus RT. One benefit of RT is the ability to treat widely (and deeply), to encompass microscopic subclinical spread that, if surgically approached, would leave a large defect, necessitating reconstruction.

Metastatic Nodal SCC

A minority (<5%) of patients with head and neck SCC develop metastatic SCC to the PG nodes and/or cervical nodes. Patients invariably have a past history of treated NMSC of the head and neck, and most will have an identifiable index lesion from which the metastatic SCC arose. Best practice for patients with metastatic cutaneous nodal SCC is appropriate surgery and, in most cases, adjuvant RT.[56] Very few patients will not benefit from combined treatment, excluding those with a single involved node without extracapsular spread and who are not immunosuppressed.[90] The addition of adjuvant RT is well documented to improve locoregional control and survival.

Surgery

For patients with metastatic SCC to cervical lymph nodes, surgery has traditionally involved a modified radical neck dissection. However, more recently, there has been a trend toward selective neck dissection in patients with a low burden of metastatic cancer (N1 and N2), with the aim of reducing surgical morbidity.[91–95] A recent Australian study of patients with SCC reported no statistically significant difference in 5-year overall survival (61% vs. 57%) or 5-year disease-free survival (74% vs. 60%) for selective neck dissection or radical neck dissection, respectively.[96] Recent data have simplified the relationship between the site of the primary SCC (if identified) and nodal metastasis, allowing more selective treatment of the neck, both surgically and with adjuvant RT. In a study of patients with an anterior facial SCC, there were metastases to level I nodes in 17.9%, whereas only 5.4% of

patients were identified with metastatic SCC in level V lymph nodes.[61] When no metastases were identified in level II lymph nodes, only 6% of patients with an anterior facial primary SCC had metastatic SCC in level I. Involvement of level II lymph nodes is, therefore, a predictor of metastatic disease in level I cervical nodes. Furthermore, patients with metastases in levels II/III were significantly more likely to have metastatic cancer in levels IV/V than were patients without levels II/III lymph node involvement (33.3% vs. 6.7%, respectively; $p < 0.001$).[61] Examination of primary site subgroups of patients reported 15.8% of posterior facial, 2.7% of anterior facial, and 0% of external ear SCC, without level II/III metastases, but had levels IV/V lymph node involvement.[61]

In that study, 21% of patients who underwent parotidectomy and elective neck dissection for a clinically N0 neck had pathologically proven metastatic cancer in cervical lymph nodes.[61] Importantly, in the same study, patients with metastatic SCC to the parotid region and a clinically N0 neck had no metastases in levels IV/V in the absence of pathologic metastatic disease in levels II/III. Therefore, selective neck dissection of cervical lymph node levels II and III is recommended for patients undergoing parotidectomy for metastatic SCC.

Parotid nodes are the most frequent site for metastasis from a primary SCC. Metastases travel via a rich lymphatic network from the primary site to 15 to 20 superficial periparotid lymph nodes and 4 to 5 lymph nodes within the deep parotid lobe. Involvement of parotid lymph nodes has implications with regard to prognosis and management. All patients with metastatic SCC to the parotid region and a clinically node-negative neck should undergo parotidectomy and ipsilateral selective neck dissection.[61,97,98]

Parotidectomy usually involves superficial lobectomy with preservation of the facial nerve (FN). Less commonly, an extended parotidectomy is required, with sacrifice of either the main trunk or at least one of the main branches of the FN. If the FN is sacrificed, facial reanimation is recommended either immediately or as a delayed procedure. As resection rarely achieves margins >5 mm, the FN should be sacrificed only in the presence of preoperative FN palsy or gross involvement at the time of operation. Consideration should be given preoperatively to both the extent of the resection of involved skin overlying the parotid and reconstructive options, including local and free flap reconstruction.

One study examined outcomes for patients with involved margins, in whom the tumor had been dissected from the FN.[99] Data on 15 patients treated with nerve-sparing surgery plus adjuvant RT from a database of 176 patients were analyzed. Two patients had residual FN palsy despite nerve-sparing surgery. Three patients developed recurrent cancer in the parotid bed, which was salvaged successfully with radical surgery and FN sacrifice. It was concluded that 10 of 15 patients had normal FN function posttreatment with no difference in disease-specific survival when compared with patients who had clear or close margins. Therefore, patients without macroscopic involvement of the FN, but with close margins, can still undergo nerve-sparing surgery provided adjuvant regional RT is delivered.

Reconstruction

Primary SCC should be excised with a macroscopically clear margin of 1 cm. If there is sufficient skin laxity, and the defect is not too large, primary closure can be performed, ideally parallel to the skin's natural relaxed skin tension lines. For larger defects, primary closure will not be possible, and the wound may be left to granulate by secondary intention. Concave areas, including the conchal bowl, perialar, and medial canthal regions, are amenable to healing by secondary intention. Reconstruction of the defect, to restore form and function, is a more viable alternative. The reconstructive ladder of healing by secondary intention, primary closure, skin grafting (Fig. 8.7), local flap, distant flap, free flap (Fig. 8.8) (including composite graft), and prosthesis should be followed. Local flap reconstruction follows the principle of replacing like with like, ideally from the same esthetic subunit of the face, and is the workhorse technique for repair of facial defects. Donor site morbidity should be kept to a minimum.

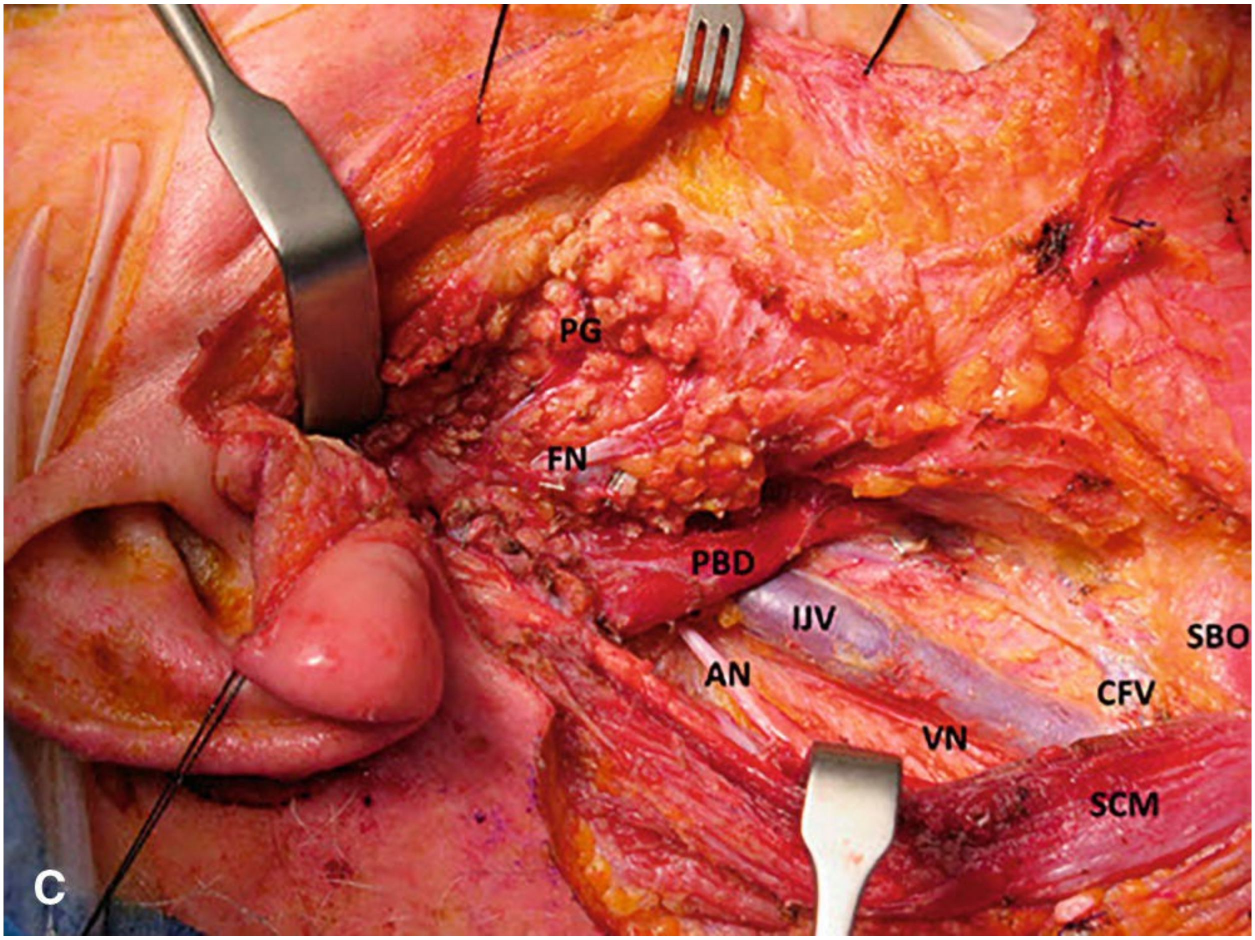
Figure 8.7. *A split-thickness* skin graft covering a large defect following wide local excision of an SCC. Note that as long as healing has been achieved, most skin grafts tolerate adjuvant radiotherapy well with a minimal risk of graft loss. Radiotherapy, if required, usually commences 4 to 6 weeks post excision allowing adequate time for healing.

Figure 8.8. Free flap reconstruction in a patient undergoing excision of a large deeply invasive right preauricular SCC.

Small defects of the nose can be reconstructed with a skin graft, or bilobed or paramedian forehead flap, whereas a rhomboid or V–Y flap can be used to reconstruct cheek defects. Larger defects of the cheek or tail of parotid can be repaired with a cervicofacial rotational flap (Fig. 8.9A–G). An Abbe-Estlander flap can be used to reconstruct small defects of the lip, whereas larger ones may require a Karapandzic flap.


A


B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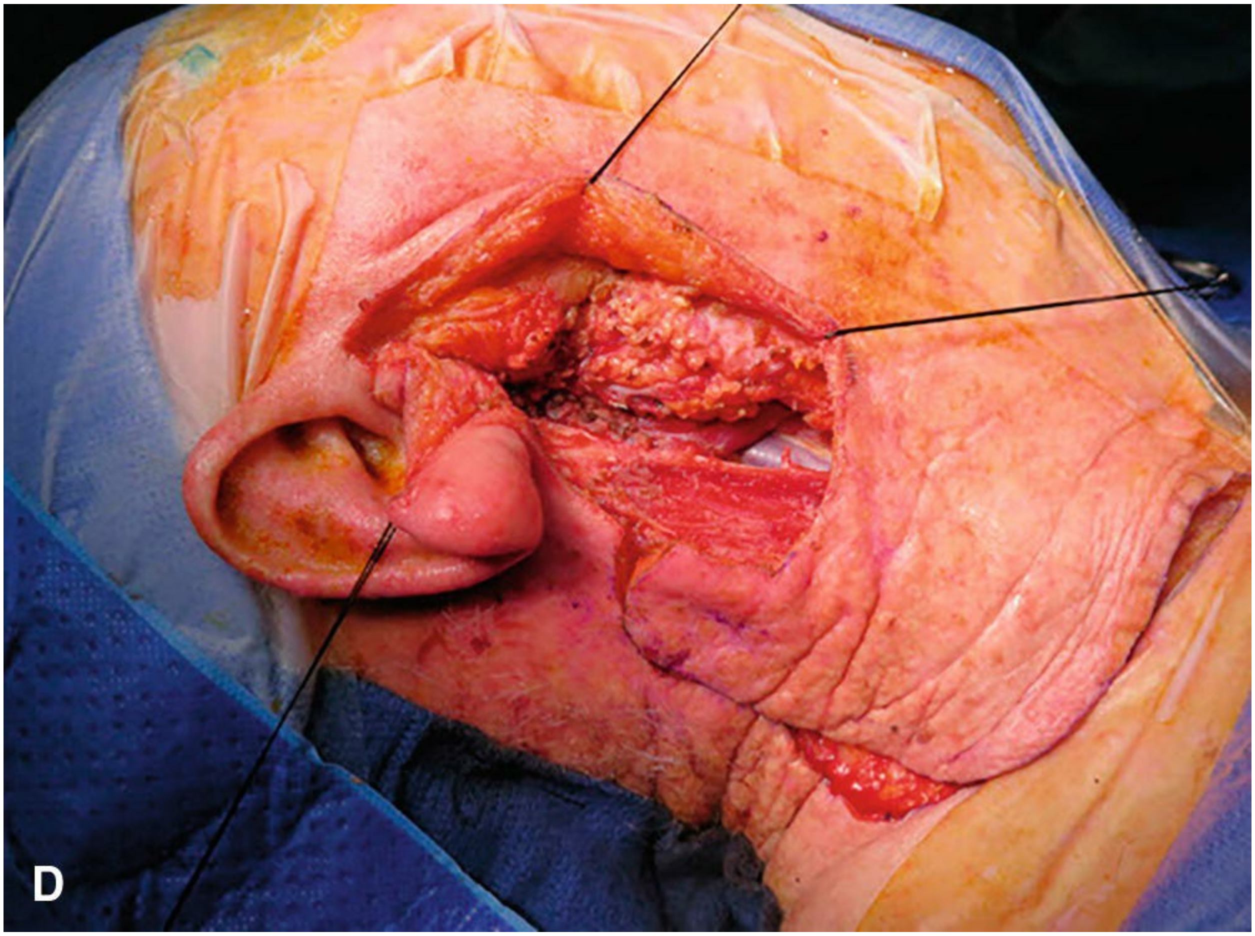
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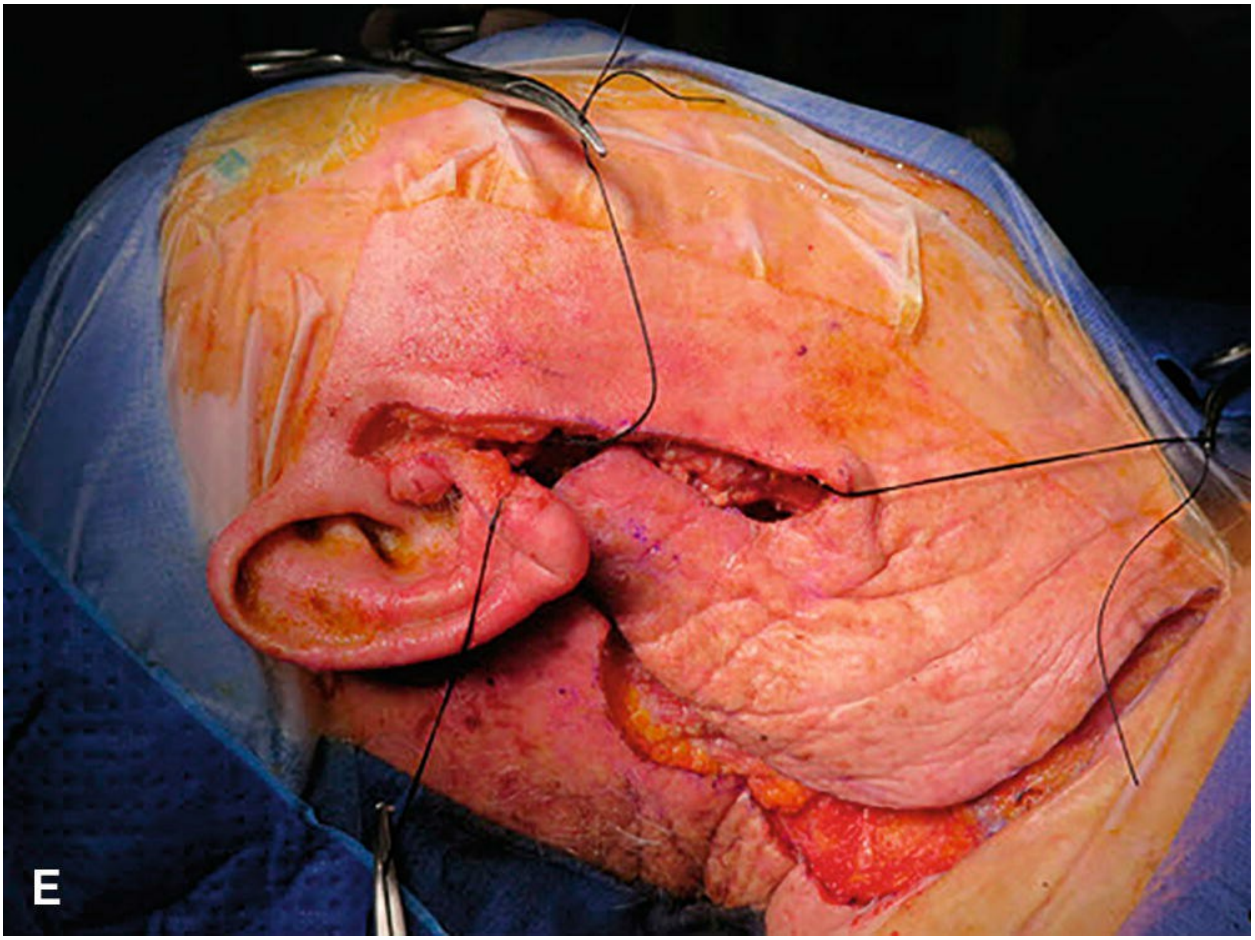
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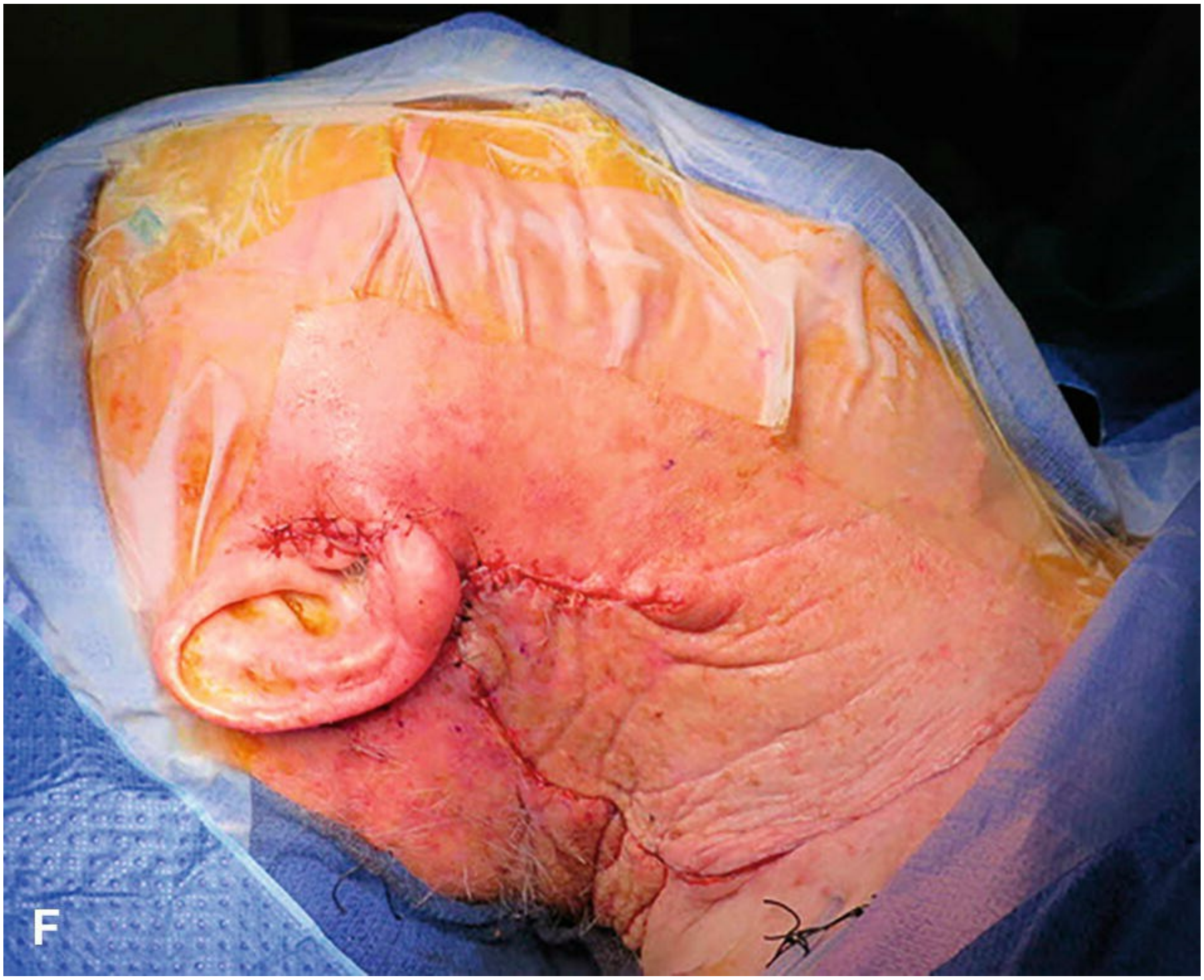
F

Figure 8.9. A: A 77-year-old male with an SCC metastatic to the tail of his right parotid gland. No primary cutaneous SCC could be identified in the head and neck region. **B:** Preoperative surgical markings, demonstrating the approach for a parotidectomy. The tumor will be removed with a margin of skin, leaving behind a defect in the skin, which will be replaced by a rotational cervicofacial skin flap. **C:** Intraoperative view of the tumor having already been dissected from the parotid gland (PG), including an appropriate parotidectomy, exposing the underlying branches of the facial nerve (FN). A level II to III neck dissection was also performed (subsequently pN0). Anatomic structures displayed include the posterior belly of digastric (PBD), sternocleidomastoid (SCM), accessory (AN) and vagus (VN) nerves, superior belly of omohyoid (SBO) (marking the lower limit of the neck dissection), and internal jugular (IJV) and common facial (CFV) veins. **D:** Cervicofacial skin flap prior to its rotation anteriorly to fill the skin defect removed with the tumor. **E:** The mobilized and tension-free cervicofacial skin flap placed into the defect prior to being sutured in place. **F:** The wound and defect are closed with a cervicofacial rotation skin flap as the skin posterior to the original

tumor is rotated anteriorly. **G:** Wound appearance at 3 weeks postoperatively.

Restoration of function is important, for instance, when the FN is invaded by metastatic cutaneous intraparotid cancer, necessitating radical parotidectomy. Complete rehabilitation addresses adequate eye closure, facial symmetry, oral competence, nasal valve support, normal facial contour, appropriate skin color match, and eventual facial muscle tone. The anterolateral thigh free flap can be used to approach some of the above, with a fasciocutaneous flap to restore the contour of the cheek. Facial function can be reconstructed using static or dynamic means. Static techniques include brow lift, tarsorrhaphy, and gold weight to the tarsal plate of the upper eyelid. Dynamic techniques encompass cable grafting of the FN and muscle transposition. Cable grafting can use the great auricular, sural, or vastus lateralis nerves. Fascia lata slings, with transposition of the temporalis tendon, can help to maintain the oral commissure, whereas anterior belly of digastric transposition enables lower lip eversion.

Provided principles of reconstruction, with regard to esthetic facial subunits and knowledge of the various rotational and free flaps, are followed, adequate and acceptable restoration of both cosmesis and function can be achieved.

Radiotherapy of the Primary Site

RT to a primary SCC avoids an operation and the associated surgical morbidity, scarring, and requirement for reconstruction and has the advantage of treating tissue extensively and deeply (5 to 30+ mm margins) that may otherwise require excision (+/− reconstruction). An obvious benefit is improved cosmesis and preservation of function, especially in situations in which a flap or graft is required.[100] RT is particularly beneficial in areas of the midface where excision and reconstruction could have a greater impact on form and function [e.g., the periorbital region (especially the medial canthus), lower eyelid, nose (in particular the ala and tip), nasolabial fold, lip, and chin].[101] Elderly patients with significant comorbid conditions are also often better treated with RT (Fig. 8.10). A typical course of fractionated RT ranges from 10 to 25 minutes once per day (minus weekends) with 10-minute outpatient treatments (or fractions). However, in older, sicker patients, fewer (3 to 5) fractions can be used. Younger patients (<50 years) can still receive

RT, but the late (>5 years) in-field cosmetic outcome (i.e., hypopigmentation, telangiectasia, epidermal atrophy), especially with continued unprotected sun exposure, may not be ideal. The risk of an in-field radiation-induced malignancy many years after small-field cutaneous RT is theoretically possible, but rare, and should not be a reason to avoid RT in younger patients.

Figure 8.10. Patient from Figure 3, now 5 months post completion of definitive radiotherapy. He has achieved an excellent cosmetic outcome with acceptable acute and self-limiting toxicity from his treatment.

Patients with locally advanced (T4) primary skin cancers involving bone and cartilage, muscle, or nerves can still be treated and cured with definitive RT. In a study of 21 patients with T4 NMSC treated with megavoltage RT, almost 60% achieved disease control, with many treated by IMRT.[102] The use of newer technology such as IMRT, in select patients with advanced NMSC, may allow the delivery of higher doses of RT, yet minimizing the side effects of treatment. Similarly, in 25 patients with an advanced NMSC and treated with helical tomotherapy (a form of IMRT) delivering doses between 50 and 70 Gray (Gy), the authors documented complete clinical remission in 88%.[103]

In a study of 28 patients with advanced NMSC (5 cm median size) treated palliatively, 24 Gy were delivered over 3 weeks. The authors reported an alleviation of symptoms in 83% of assessable sites and a complete response in 36% of patients.[104] Alternatively, large single fractions of 10 to 15 Gy may also be appropriate in debilitated patients in a nursing home with large neglected lesions that are often painful, bleeding, and infected.

The sun-exposed lower lip is a site ideally suited to treatment with definitive RT where extensive surgery could result in significant morbidity from microstomia (reduction in size of oral commissure). RT can achieve excellent preservation of oral function and achieve an outcome comparable to surgery. Treatment with either RT or surgery has been documented to have similar efficacy in retrospective studies. Surgical series report disease control in 85% to 90% of cases, with local recurrence rates of 5% to 10% and regional relapse rates of ~5%.[105] The Westmead hospital group analyzed data on patients treated with surgery, RT, or surgery + adjuvant RT and documented a 5-year relapse-free survival (RFS) of 51%, 87%, and 92%, respectively, noting that the lower RFS for surgical patients was often secondary to a higher local relapse when there was incomplete resection. Most patients, however, were successfully salvaged, and consequently, the 5-year overall survival for RT versus that for surgery was similar (79% vs. 83%).[106]

Most clinicians accept excision as an excellent option, particularly in

younger patients, as wedge resection with primary closure is often curative. In patients with more extensive cancer, where wedge excision and primary closure may result in microstomia, local flaps may be required to achieve oral competency. RT is often considered an excellent option for elderly patients, many of whom suffer from comorbidities, as it obviates the need for a general anesthetic, surgery, and hospitalization and offers the advantage of preservation of lip function and cosmesis, making it also an option for younger patients, particularly if complex reconstruction is anticipated.

Regional Radiotherapy

In a study of 74 Australian patients with metastatic SCC to cervical lymph nodes, those treated with surgery and adjuvant RT had a lower recurrence rate (15% vs. 77%) and better 3-year disease-free survival (70% vs. 45%) compared with patients treated with surgery alone.[84] In a review of 122 Australian patients, there was a 5-year overall survival of 66% with adjuvant RT compared with 27% with surgery alone.[56] Patients should receive 60 Gy in 2 Gy fractions to an operative bed and 50 Gy in 2 Gy fractions to undissected regions, including the lower neck. Patients with metastatic SCC to the parotid region, with a clinically N0 neck, who undergo parotidectomy and selective neck dissection, and who are found to have pathologically evident metastasis in the neck require adjuvant RT to both the parotid bed and ipsilateral neck. Selective RT only to the parotid bed may be considered in patients with a pathologic N0 neck.[78,89] Despite best practice, 10% to 15% of patients will develop recurrence, most often regional, with only a minority (20% to 30%) successfully salvaged.

Prognostic Factors

The Westmead Hospital Group published a 4-factor prognostic scoring system, the ITEM score, which considers immunosuppression, treatment, extracapsular spread, and margins.[107] In this study, a cohort of 250 patients was analyzed to identify relevant patient, tumor, and treatment factors to examine prognosis in patients with metastatic SCC of the head and neck. Twenty-eight percent of patients developed recurrence. Those treated with combined modality had a lower recurrence rate than those treated with either surgery or RT alone (17% vs. 48%, respectively). Regional recurrence occurred in 73% of patients, whereas distant metastasis as the first

presentation of recurrence was uncommon and occurred in only 9 (13%) cases. Patients failing treatment did so within a median time of 8 months, and 73% died of their disease. This demonstrates the importance of achieving control of nodal metastasis.[107] Using coefficients of the ITEM variables as weights, risk scores were calculated for each patient. This allowed the development of risk groups based on cutoff scores. Patients with a score ≤2.6, >2.6 to ≤3, or >3 were, respectively, classed as low, medium, or high risk for dying of disease. Scores demonstrated that the chance of dying of disease according to this novel prognostic classification at 5 years was 6%, 24%, and 56%, respectively. This is a simple and easy system that can be used clinically to prognosticate and allows identification of patients at risk of a poor outcome.

Sentinel Node Biopsy

Sentinel lymph node biopsy (SLNB) offers the potential to identify occult (or subclinical) metastases and possibly influence outcome. The lower incidence of cutaneous metastatic nodal SCC and the need to identify high-risk patients better remain issues. Schmitt et al.,[108] in a meta-analysis, documented 12.3% of microscopic nodal metastases detected by SLNB in high-risk cutaneous SCC, with a false-negative rate of 2.6%. They highlighted the ambiguity of the term “high risk” and undertook a comparative analysis—one with the TNM from the AJCC-7 and another with an “alternative TNM System” proposed by Jambusaria-Pahlajani et al.[109] This “alternative tumor staging system” used risk factors identified to predict more than one outcome in a multivariate analysis, that is, tumor thickness >2 mm, Clark level of IV or higher, location on ear or non–hair-bearing (vermillion) lip, poor differentiation, and tumor diameter of 2 cm or greater. Utilizing the AJCC-7 criteria, 11.2% (13/116 patients) with a T2 cutaneous SCC had positive sentinel lymph nodes (SLNs), rising to 60% (3/5 patients) in patients with T4 tumors. All patients with a positive SLN had cutaneous SCC > 2 cm in diameter. Using the alternative TNM System, no cases (0/9 patients) of a positive SLN were documented in the T1 primary (0 risk factors), 7.1% (6/85 patients) in T2a lesions (1 risk factor), and 29.4% (5/17 patients) in T2b lesions (2 to 3 risk factors). The authors reported a statistically significant difference between the proportions of T2a and T2b ($p = 0.02$).[108] In view of these data, it would be reasonable to consider the 2-cm cutoff as an

independent risk factor for considering SLN biopsy, and patients with *more than* two risk factors (definition of T2b for the Alternative TNM system) may also warrant SLN biopsy. These results suggest that select high-risk patients may benefit from SLN biopsy, but further research is required (Fig. 8.11).

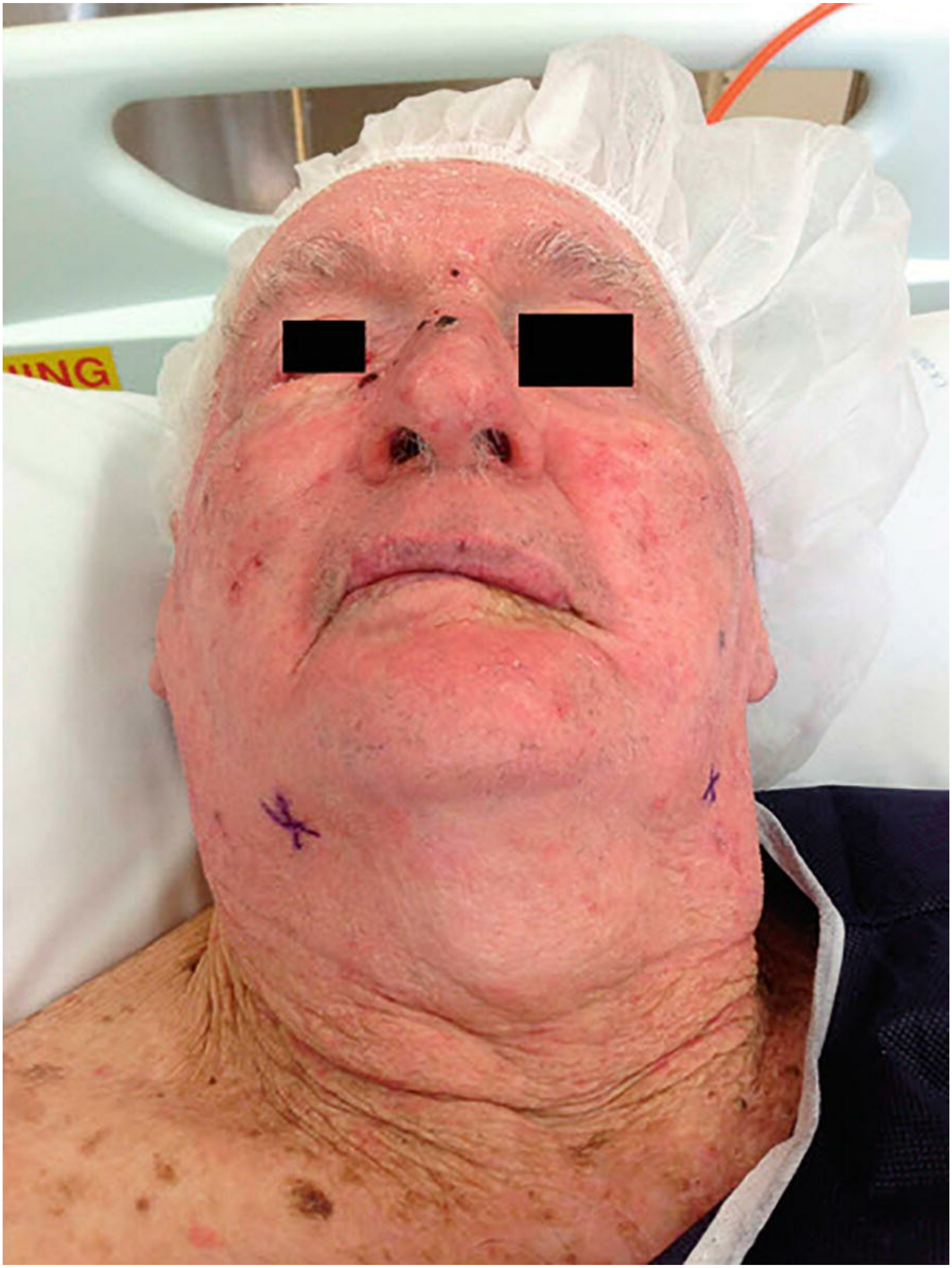

Figure 8.11. A 90-year-old male undergoing sentinel lymph node (SLN)

biopsy for a nasal 8-mm MCC. The patient had two SLNs located in his bilateral upper neck in his level Ib nodes (as marked). Both SLNs were positive for microscopic deposits of MCC, and he proceeded to radiotherapy to these sites and his nose.

Adjuvant Chemotherapy

Despite surgery and RT, a minority of patients will develop recurrence, most often regional in the treated parotid and/or neck. Any means to improve regional control is therefore likely to improve survival. A randomized controlled trial undertaken in Australia and New Zealand, and close to accrual in 2014, evaluated concurrent low-dose weekly carboplatin chemotherapy and RT as an adjuvant therapy in high-risk patients [Postoperative Concurrent Chemoradiotherapy Versus Postoperative Radiotherapy for Cancer of the Head and Neck (POST) trial]. The addition of concurrent platinum-based chemotherapy as a radiosensitizer is well documented in mucosal SCC, and the mature results of the POST trial may influence future management in these patients.

Targeted Treatment

Many cutaneous SCCs overexpress epidermal growth factor receptor (EGFR), and targeted treatment using monoclonal antibodies is an emerging option in certain patients with advanced (inoperable/incurable) disease. In some cases, dramatic results have been obtained using this relatively nontoxic treatment, although responses may be short-lived. In a study of 16 patients treated with single-agent panitumumab, the overall response rate was 31% with a 6-week disease control rate of 69%. Adverse events were recorded in all patients, most experiencing fatigue, cutaneous reaction, and nausea.[110] Analogous data in patients with mucosal SCC has suggested a beneficial outcome in combining RT and cetuximab. In a series of 16 patients with unresectable cutaneous SCC receiving combined RT and cetuximab, the authors documented an overall response rate of 64%, including complete response in 36%. Median progression-free and overall survival were 6.4 and 8 months, respectively, and most patients experienced a grade 3/4 reaction.[111]

Hedgehog pathway inhibitors have been used to exploit up-regulation of the hedgehog signaling pathway, seen recently in BCC patients with genetic

alterations. A new oral drug, vismodegib, inhibits this pathway and may offer a potentially new treatment for patients with advanced (inoperable and/or previously treated) and metastatic BCC and for those with Gorlin syndrome (basal cell nevus syndrome). A recent study reported a complete response of 21% in eligible patients, although the median duration of response was short (7.6 months) and serious adverse effects, even death, were reported.[112] With further research, it is likely that the outcome for these patients will improve with molecular inhibition of the hedgehog signaling and other pathways.

Merkel Cell Carcinoma

MCC is an aggressive neuroendocrine cutaneous malignancy that often manifests as a rapidly enlarging firm, painless, pink-red, dermal-based nodule, frequently on the head and neck (50% to 60%) or extremities/trunk in older (>60 to 70 years old) Caucasians.[113] In contrast to other types of NMSC, MCCs frequently arise in women (Fig. 8.12). It is often misdiagnosed, as it may resemble BCC or amelanotic melanoma. The median size of the primary lesion at diagnosis is ~2 cm, and the incidence of clinical nodal involvement at presentation is ~20% to 25%, although the risk of harboring occult nodal disease is high (30% to 40%). A minority of patients (10% to 15%) will have node metastases but without an identifiable primary (index) lesion and have a better prognosis compared to patients presenting with a concomitant primary and nodal metastases.[114] MCC has a high propensity to spread to regional lymph nodes and distant sites (usually in the relapse setting) and has a cause-specific mortality of 25% to 50%, despite treatment.

Figure 8.12. A 72-year-old female having undergone recent wide local excision of a 15-mm left cheek MCC presenting now with 2-cm nodal metastases in her left parotid. The patient proceeded to urgent radiotherapy to encompass her excision site and involved parotid and upper neck using high-dose electrons (50 Gy in 20 fractions). She achieved in-field locoregional control but died 5 months later from metastases to the liver.

Etiology is secondary to chronic ultraviolet B (UVB) sun exposure, and more recently, the identification of the Merkel cell polyomavirus (MCV or MCPyP),[115] first identified in 2008, with some studies identifying MCV integrated into the host's genome in 80% of cases, but reported to be much less (20%) in other studies. It is postulated that MCV in certain populations (e.g., Australians) may play less of a role in the development of MCC compared to the mutagenic consequences of chronic UVB exposure. The virus is considered part of normal human flora and is also present in healthy tissue from the general population. The role of MCV in the etiology and prognosis is under investigation. The increased risk of developing MCC in patients immunosuppressed due to CLL may possibly be explained secondary to MCV infection. MCC is highly immunogenic, with a higher incidence in immunosuppressed patients (e.g., transplant recipients and hematologic malignancy), who subsequently have a worse outcome.[116]

Prognostic Factors in MCC

The presence of clinical lymph node metastases (stage III) is the most important prognostic factor. Patients identified as having pathologically proven occult (or microscopic) metastases also have a worse prognosis compared with patients with MCC confined to the primary site. Increasing size of the primary cancer is moderately predictive of outcome, although other tumor variables such as thickness and Clark level are less helpful. Recently, the identification of LVI[117] has been reported as predictive for the development of metastases.

TNM Staging and Prognostic Risk Grouping

Stage at diagnosis is prognostic (AJCC 7th edition staging manual, Table 8.3). Patients with stage I (T1N0) and II (T2-4N0) with pathologically evaluated negative lymph nodes have a better survival compared with clinically node-negative patients.[118] Of the 3 stages documenting nondistant spread, stages I and II are classified by tumor size (T1 ≤ 2 cm, T2 > 2 to 5 cm, T3 > 5 cm) and within each stage further categorized (A, B) depending on whether draining nodes have been evaluated pathologically or clinically. Due to the high false-negative rate (30% to 40%) for detecting occult metastatic nodal metastases clinically, patients with the same stage, but with clinically staged nodes, have a documented worse prognosis compared to

patients who undergo pathologic staging of nodes (e.g., SLN biopsy). Patients with stage III disease have pathologically confirmed nodal metastases and are further divided into those with micrometastases (i.e., occult) or macrometastases (clinically detectable).

Table 8.3 Staging for Merkel Cell Carcinoma (7th Edition of AJCC Staging Manual)

Tumor		Node		Metastasis	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor (e.g., nodal/metastatic presentation without associated primary)	N0	No regional lymph nodes metastasis	M1	Metastasis beyond regional lymph nodes
Tis	*In situ* primary tumor	cN0	Nodes negative by clinical examination (no pathologic node examination performed)	M1a	Metastasis to skin, subcutaneous tissues, or distant lymph nodes
T1	≤2 cm maximum tumor dimension	pN0	Nodes negative by pathologic exam	M1b	Metastasis to lung
T2	>2 cm but ≤5 cm maximum tumor dimension	N1	Metastasis in regional lymph node(s)	M1c	Metastasis to all other visceral sites
T3	>5 cm maximum tumor dimension	N1a	Micrometastasis		
T4	Primary tumor invades bone, muscle, fascia, or cartilage	N1b	Macrometastasis		
		N2	In-transit metastasis		

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Role of RT in Patients with Early-Stage MCC

The propensity for MCC to recur after local excision and the excellent response to RT have meant that many publications have reported a statistical and clinical benefit in reduced locoregional recurrence, with the addition of wide-field (2- to 3-cm field margins) adjuvant RT.[119] Locations such as the head and neck often result in close or positive margins of resection in an attempt to maintain acceptable cosmetic outcome and/or function. There are no randomized studies addressing the benefit of RT versus surgery. Some clinicians may omit adjuvant RT for patients who have had adequately excised (margins > 10 mm) small (<2 cm) cancers that do not have LVI present and are pathologically node negative. In many series, patients with these low-risk features make up only a minority, and therefore, the majority

of patients at these particular centers would undergo excision and adjuvant RT. Proponents of combined treatment advocate margin negative surgery, without the need for wide 5- to 10-mm margins, to be followed by RT.

Target Volume

The target volume for MCC consists of the excision site (with 3- to 4-cm margins), in-transit tissue, and at least the first echelon nodes (may consider next level as well). When a lesion is close to critical structures (e.g., orbit), narrower margins and appropriate shielding need to be considered.

Management of Lymph Nodes in Clinically Node-Negative Disease

Studies using SLN biopsy report positive occult nodes in 30% to 50% of cases.[120] No single clinicopathologic feature strongly predicts for the risk of harboring occult metastases, and clinical staging alone, including relevant investigations, will not detect small volume (<5 mm) or microscopic MCC nodal metastases. Studies clearly show that patients with a positive SLN biopsy have a worse outcome compared with a negative biopsy and will benefit from treatment to the nodal basin. Those not investigated pathologically have a lower survival compared to patients staged pathologically. Lesions located on the trunk or extremities may particularly benefit from SLN biopsy as treatment of a positive nodal basin may need to be discontinuous from the primary site, unlike the head and neck where often the primary site, in-transit tissue, and nodes can be approached with an en bloc RT field. Patients not undergoing SLN biopsy should be considered for elective nodal treatment (e.g., surgery or RT) or alternatively be monitored very closely.

Management of Lymph Nodes in Clinically Node-Positive Disease

Numerous studies reporting RT alone in the setting of macroscopic MCC have documented durable in-field control of 75% to 85% using doses of 50 to 60 Gy.[121] Most patients with metastases to the cervical lymph nodes will still be candidates for adjuvant nodal RT after lymph node dissection (multiple nodes, extracapsular spread, close soft tissue margins). A recommendation

for RT alone to patients with technically operable low volume (~3 cm maximum dimension) is not standard or routinely recommended, but avoids the need for hospitalization and the morbidity of surgery of the lymph nodes. The addition of adjuvant RT to axilla/groin following surgery also increases the risk of limb edema. Patients with medical comorbidity may also experience postoperative complications, delaying the commencement of adjuvant RT.

Role of Chemotherapy in the Definitive Setting

The benefit of systemic chemotherapy in the definitive setting remains unclear and unproven.[122] Similar to small cell carcinomas arising from other sites such as the lung, regimens using carboplatin and etoposide have been investigated. Numerous single-arm studies administering chemotherapy during (concomitantly) and after (adjuvantly) RT have documented the feasibility and efficacy of combined chemotherapy/RT. However, chemotherapy-associated mortality and morbidity are not inconsequential in this group of older patients, many suffering from multiple comorbidities.

OTHER RARE TUMORS

Malignant Adnexal Tumors

Malignant tumors of the adnexa arise from the pilosebaceous unit and eccrine and apocrine sweat glands. These tumors tend to be indolent and rarely metastasize. Microcystic adnexal carcinoma (MAC), malignant cylindroma, sebaceous carcinoma, primary cutaneous mucinous carcinoma, pilomatrix carcinoma, and adenoid cystic carcinoma show a predilection toward the head and neck region.[123]

They usually appear as a solitary, flesh-colored nodule. MAC can infiltrate nerves and has a 10-year survival rate approaching 97%.[124] Risk factors include previous irradiation and immunosuppression.[125] Sebaceous carcinomas usually arise from orbital sebaceous glands, typically the meibomian glands of the tarsal plate.[126] Apocrine carcinoma is more common in middle-aged females, occurring on the eyelid, scalp, and ear.[127] Primary cutaneous mucinous and adenoid cystic carcinomas are more

common in the elderly, the former occurring most often on the eyelid, cheek, and scalp[128] and the latter on the scalp.[129]

Once diagnosis is confirmed by biopsy, these tumors are excised with a 1-cm margin. RT can be given adjuvantly for positive margins or presence of PNI.[103,124]

Angiosarcoma

This tumor is a rare (<1% of all head and neck malignancies[130]), but aggressive, malignancy, most commonly arising on the scalp and upper forehead of elderly Caucasian males.[131] Previous RT and chronic lymphedema are risk factors.[132] It can be multifocal, presenting as bluish nodules, plaques, or flat infiltrating areas. It often presents too late for effective surgical excision. Only 7% of patients have nodal disease.[132] Surgery and wide-field RT are the mainstay of treatment, but recurrence at the margins of the RT field is common. It metastasizes hematogenously, in which case palliative chemotherapy is appropriate, enabling 1- to 5-month survival. Five-year survival is 10% to 30%.[131]

Kaposi Sarcoma

This rare cutaneous spindle cell tumor is considered to be derived from endothelial cells. It occurs more frequently in patients with acquired immune deficiency syndrome (AIDS), in whom the clinical course is more aggressive, but is up to 100 times more frequent in organ transplant patients.[133] Cutaneous lesions typically occur in the head and neck region as brown, pink, or red macules, papules, nodules, or plaques. There are often concurrent mucosal lesions.

Optimal control of AIDS is required, but treatment of the lesions includes RT,[134] cryotherapy,[135] excision by scalpel or laser,[136] intralesional or systemic vinca alkaloid,[137] or topical retinoids.[138]

CONCLUSION

Patients with BCC can expect to be cured of their disease. Patients who develop either high-risk SCC or MCC are at a risk of morbidity and,

potentially, mortality. Exposure to UV radiation is the most important risk factor for the development of NMSC, but there are other factors, including immunosuppression, which increase the likelihood of a poor outcome. A simple, accurate, and universally applied staging system is vital when managing these patients. Ongoing research is required to develop therapeutic strategies, such as adjuvant chemotherapy and targeted molecular therapy, for patients with high-risk disease. Contemporary best practice management of primary and metastatic cutaneous SCC of the head and neck includes a combination of surgery and/or external beam RT.

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9 Melanoma of the Head and Neck

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Although melanoma accounts for only 5% of cutaneous cancers diagnosed each year, it is the most lethal form, accounting for over 75% of deaths attributed to skin cancer. Approximately 25% of all cutaneous melanomas arise in the head and neck (HN) region.[1] The dramatic increase in melanoma incidence and mortality over the past two decades has led to significant economic burden.[2] In 2010, the total direct cost of treating melanoma in the United States exceeded $2.3 billion.[3] The leading cause of melanoma remains intense sun exposure; consequently, it is a cancer of young as well as older adults. Melanoma ranks second only to testicular cancer in loss of average adult life-years per fatality and a loss of ~$3.5 billion in productivity.[4] These startling melanoma statistics underscore the importance of prevention, accurate staging, and clinical trials.

EPIDEMIOLOGY

The incidence of cutaneous melanoma in the United States continues to rise at epidemic proportions with 137,990 new cases of melanoma estimated in 2014 (61,300 noninvasive; 76,690 invasive).[2,5] This rate has consistently increased 2.8% per year since 1981. By 2015, it is estimated that 1 in 50 Americans will develop a melanoma in their lifetime.[6] A slight male predominance has been consistently reported throughout the literature.[7,8]

Although the mortality rate of various cancers has declined, mortality from melanoma has risen by 3% each year since 2004. 9,710 Americans will die from melanoma this year, an estimate that averages to approximately one

patient per hour.[2] Melanoma typically arises in the fifth and sixth decade.[7] However, this statistic is misleading because one in four new melanoma cases will present before the age of 40 years. The increasing incidence among younger patients, especially women, is attributed to sun worshiping tendencies and indoor tanning.[9] Melanoma is the most common cancer for young adults aged 25 to 29 years, the second most common cancer for women aged 30 to 34 years, and the second most common cancer in ages 15 to 14.[5] Patients in the pediatric age group account for ~1.66% of the HN melanoma cases, with patients being diagnosed as young as 4 years old.[10,11]

PATHOPHYSIOLOGY

Melanocytes are dendritic cells of neural crest origin, located at the epidermal–dermal junction.[12] They contain cytoplasmic organelles termed *melanosomes*, which synthesize *melanin*. The melanin is degraded and distributed to surrounding keratinocytes where the granules form supranuclear caps within the keratinocytes for protection from damaging ultraviolet radiation (UVR).[13] The photoprotective property of melanin results from the absorption of both UVR photons and the oxygen radical by-products of UVR.[14,15] This protective role of melanin is evident during tanning: UVR exposure increases melanogenesis, which leads to skin darkening. The protective layer of melanin serves as an endogenous sunscreen, persisting for ~3 weeks following exposure.[15]

All individuals, regardless of ethnicity, have approximately the same number of melanocytes. It is a difference in the number, distribution, and density of melanin granules within keratinocytes that account for racial variation in skin color.[12] Melanocyte density varies throughout the body. Within the HN region, the average number of melanocytes per mm^2 is 1,194 for the adult face, 1,060 for the scalp, and 926 for the neck.[12] This concentration is considerably higher compared to other anatomic sites such as the buttock and abdomen, which contain only 565 and 578 melanocytes/mm^2, respectively. The concentration of melanocytes within sun-exposed regions of the body further emphasizes the UVR-protective role of melanin.[16]

Whereas cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are associated with lifetime cumulative sun exposure,

melanoma is associated with intermittent and intense exposures common in sunburns.[17,18] It is most often diagnosed among individuals with indoor occupations, who have intermittent sun exposure only during weekends or vacations.[19] This correlation may explain the high melanoma incidence of melanoma in northern states known for long winters (Fig. 9.1). This contrast in cutaneous cancer etiology is attributed to an inherent difference in tumor cell origin. SCC and BCC both arise from keratinocytes, which undergo apoptosis in response to severe UVR damage. Throughout years of low-dose solar exposure, keratinocytes can accumulate a significant amount of unrepaired DNA damage to ultimately lead to SCC or BCC. Melanocytes, however, have not been found to undergo apoptosis, a quality that is deemed photoprotective.[20] However, this protective measure comes at the expense of increased risk for melanoma. The appearance of freckles after intense sun exposure supports this theory because freckles represent clones of mutated melanocytes and carry an increased risk for melanoma.

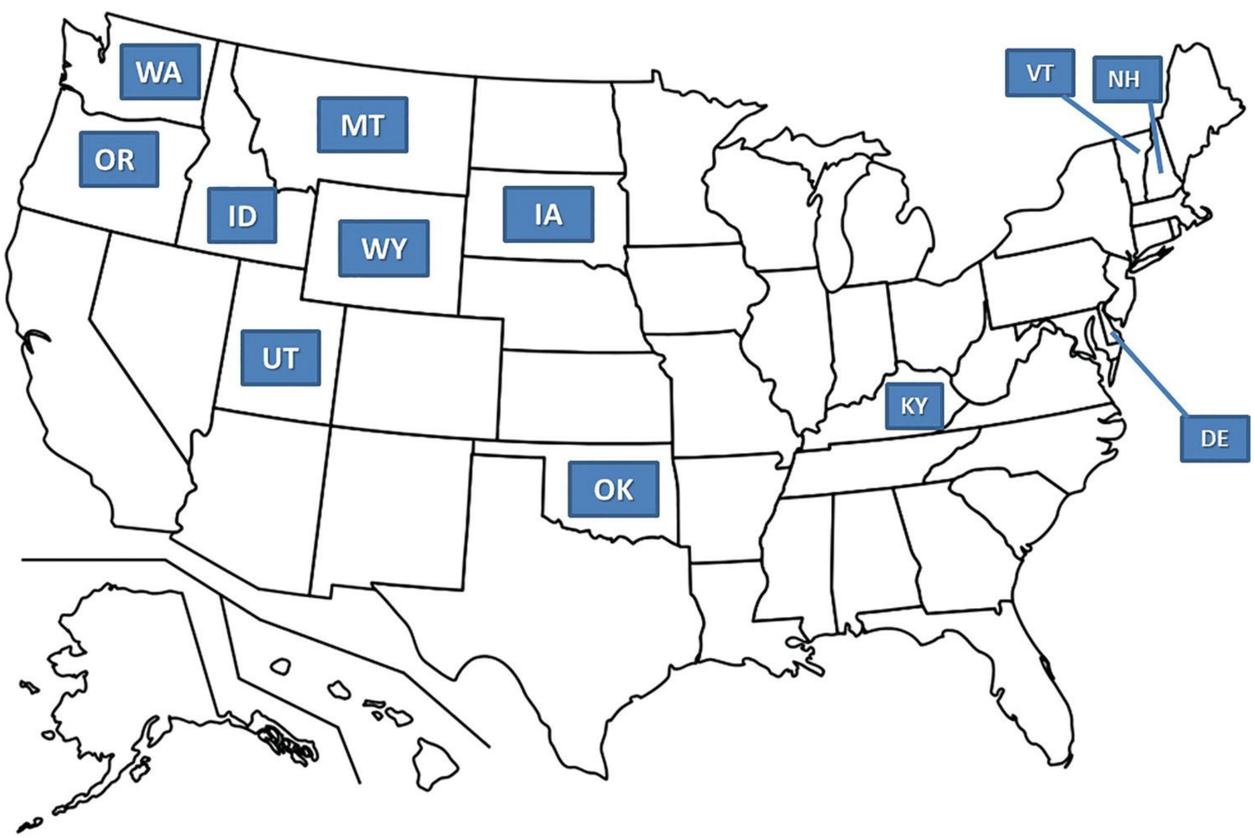

Figure 9.1. United States Center for Disease Control and Prevention (CDC) 2010 list of the highest melanoma incidence by state. Statistics include both genders and all races. Melanoma is attributed to intense, intermittent as

opposed to cumulative sun exposure, which may account for this high incidence in northern states.

ANATOMIC DISTRIBUTION

Approximately 25% of all cutaneous melanomas arise in the HN region.[1] The majority arise on the cheek, scalp, and neck.[7,8,21] Among 857 HN melanoma patients, Fisher et al.[7] found that the face and neck regions accounted for over 60% of primary tumors. An additional 26% arise from the scalp, with the ear and nose accounting for only 9% and 4% of primary tumors, respectively. This anatomic distribution was confirmed by O'Brien et al.[21] The forehead and cheek regions contain a two- to threefold higher melanocyte density compared to other anatomic sites. This difference, coupled with the increased sun exposure, likely accounts for the distribution of melanomas within the HN region.

RISK FACTORS

Table 9.1 summarizes the environmental and genetic risk factors implicated in the development of cutaneous melanoma.

Table 9.1 Cutaneous Melanoma: Environmental and Genetic Risk Factors

Environmental	Medical/Genetic
Inability to tan	*CDKN2A* (p16) mutation
Fair skin/freckling	Immunosuppression
Blue/green eyes	Xeroderma pigmentosa
Blonde/red hair	Dysplastic nevus
History of blistering sunburn	Giant congenital melanocytic nevus
Outdoor summer job	History of prior skin cancer
Tanning booth use (UV[a] radiation)	Family history of melanoma

[a]UV: ultraviolet-alpha rays (315 to 400 nm).

Adapted from Schmalbach CE, Johnson TM, Bradford CR. The management of head and neck melanoma. *Curr Probl Surg*. 2006;43:781–835. Ref.[22]

Sun Exposure

The leading cause of melanoma is sun exposure. Johnson et al. found that 81% of 1,515 patients with melanoma investigated recalled a history of at least one sunburn.[23] Recent epidemiologic trends further support the causal relationship of solar damage and melanoma. A "latitude gradient" has been reported in which the incidence of melanoma increases among similar ethnic populations as distance to the equator decreases.[17] A higher rate of melanoma has also been reported among immigrants to areas of increased solar radiation compared to native residents.[17,24]

Rigel[25] analyzed 43 melanoma risk factors among 200 patients. Two of the six key factors associated with increased melanoma risk directly related to sun exposure are three or more blistering sunburns before the age of 20 and three or more outdoor jobs during teenage years. Additional significant risk factors identified included red/blonde hair, family history of melanoma, actinic keratoses, and marked freckling of the upper back. Individuals

demonstrating one or two key factors carried a three- to fourfold increased risk for development of melanoma. The risk for melanoma increased 20-fold if a patient was found to have three or more key risk factors.

Genetics

A genetic etiology has also been implicated in the pathogenesis of melanoma.[26] Approximately 15% of patients with melanoma report a positive family history.[27] The most commonly inherited genomic abnormalities associated with melanoma is the *CDKN2A* locus, which encodes the *p16* tumor suppressor gene.[27,28] However, *p16* mutation is reported in only 0.2% of the melanoma cases diagnosed.[29] The hereditary nature of cutaneous melanoma was first described in the 1970s when Clark et al.[30] observed two families in which members acquired large dysplastic nevi, often in sun-protected regions of the body such as the scalp and trunk. They coined the term "*B-K mole syndrome*." During this same time period, Lynch et al.[31] independently reported a similar association, which they termed "*familial atypical multiple mole–melanoma syndrome*" or *FAMMM syndrome*. Today, the term "*atypical mole syndrome*" is applied to familial cases of melanoma. The syndrome is inherited in an autosomally dominant fashion. Family members carry a 10-year melanoma risk of 10.7%, which is significantly >0.62% risk reported in control patients. A 56% cumulative risk is estimated in these carriers from age 20 to 59 years. Nearly 100% of patients with atypical mole syndrome develop melanoma by age 76.[32]

Although a melanoma gene has been postulated, the genetic aspect of this disease is far more complex.[33] The first whole-genome melanoma sequence was published in 2010 and identified more than 33,000 mutations compared to the germline control.[34] Various tumor suppressors, transcription factors, and oncogene mutations have been associated with melanoma.[35] The majority of melanomas are found to harbor one or more mutations related to a kinase signaling pathway.[33] A point mutation in *BRAF*, a serine–threonine protein kinase, has been identified in 65% of melanoma cell lines and 42% of tumors.[36,37] Eighty-five percent of the BRAF mutations are associated with a single substitution (*V600*E).[37] Mutations in *NRAS*, a member of the RAS family of GTPases, have also been implicated in up to 25% of melanoma tumors.[33] The *c-KIT* gene encodes for a tyrosine kinase receptor within the

cellular membrane, and mutation of the *c-Kit* gene has been identified in 19% of melanomas arising in chronically sun-exposed regions of the body.[38] Although the genetic alterations are promising avenues for targeted therapy (see section below), it is important to realize that an estimated 30% of patients with melanoma lack a detectable genetic abnormality.[33]

In addition to the familial forms of melanoma described above, there is another syndrome associated with melanoma development termed *xeroderma pigmentosum (XP)*. XP is a rare, autosomally recessive disease associated with skin cancers including melanoma.[39] Fibroblasts in XP patients have an impaired ability to repair DNA damaged by UVR,[40] which leads to the development of multiple cutaneous malignancies including melanoma, BCC, and SCC. Patients are usually diagnosed with their first cancer before the age of 10. Despite UVR precautions, careful surveillance, and aggressive treatment, the development of skin cancers is relentless, with the majority of XP patients succumbing to cancer during their childhood years.

Immunosuppression

Numerous studies throughout the literature provide supporting evidence for a role of immunosuppression in the development of melanoma. A recent systematic review of the literature identified an association between melanoma and the following immunosuppression settings: solid organ transplant, lymphoproliferative disorders, iatrogenic immunosuppression, and human immunodeficiency virus infection/AIDS.[41] Higher rates of premalignant melanocytic nevi in the setting of transplantation, chemotherapy, and childhood leukemia lend further support of this association.[42,43] Ultimately, immunosuppressed patients warrant vigilant monitoring for skin cancer, and melanoma care must be coordinated carefully with all medical teams.

Melanotic Nevi

Although melanoma can arise de novo, ~50% of cases develop from a preexisting pigmented lesion[44] (Fig. 9.2). The vast majority of adults have at least one melanotic lesion. *Intradermal nevi* account for the majority of adult moles. *Junctional nevi* are common in childhood. This lesion appears as a flat, tan-brown papule, which is smooth and well defined. Overall, junctional

nevi are recognized as the most common premalignant nevi.[45]

Figure 9.2. Approximately 50% of melanomas develop from a preexisting pigmented lesion.

Atypical melanocytic nevi (AMN), also known as *atypical moles, dysplastic nevi, and Clark nevi*, are acquired pigmented lesions with both a clinical and histologic appearance different from that of the common mole.[46] AMN are recognized as a marker for increased risk for melanoma risk and as a melanoma precursor. They often display irregular or poorly demarcated borders. They differ from common benign nevi in that they are typically larger in size, measuring between 5 and 12 mm in diameter.

Congenital melanocytic nevi (CMN) are pigmented lesions present at birth or within the first 6 months of infancy.[47,48] Up to 6% of children are born with CMN. CMN size ultimately dictates the melanoma risk. Small CMN (<1.5 cm diameter) and medium CMN (1.5 to 1.99 cm diameter) carry

the same lifetime melanoma risk as do any other typical nevi. However, *large* CMN (≥2 cm diameter) carry an increased risk for development of melanoma, with development in an estimated 5% to 20% of individuals.[47] These melanomas are usually diagnosed in early childhood, with 70% of cancers being diagnosed before the age of 10.[49] For this reason, prophylactic excision is advocated for large CMN if the nevus is in an anatomic location amenable to surgery. Unfortunately, the large size can carry significant cosmetic, as well as psychosocial, implications.[48]

Lentigo maligna (LM) (see above) is a melanoma subtype in which the cancer is limited to the intraepidermal layer. Classified as melanoma in situ, it is deemed a precursor to invasive melanoma. The exact percentage of LMs that progress to invasive lentigo malignant melanoma (LMM), remains unknown.[50] However, the rate of progression is estimated to be between 5% and 33%.

MELANOMA CLASSIFICATION

Three histologic variants of melanoma are reported within the HN region and are outlined below. It is important to realize that melanoma subtype does not generally influence prognosis once tumor thickness and other prognostic variables such as ulceration are taken into account. For this reason, the melanoma subtype does not impact tumor staging.

Common HN Melanoma Subtypes

The majority of HN cutaneous melanomas are *superficial spreading melanoma (SSM)*, accounting for ~70% of all cases.[19] The characteristic SSM feature is color variation, which is often described as kaleidoscopic with areas of black, dark brown, tan, and blue-gray pigmentation. Areas of pink and white may be present and represent hypopigmentation secondary to tumor regression. Although SSM lesions are well circumscribed, the borders tend to be scalloped and asymmetric. Patients are usually diagnosed within their fourth to fifth decade and often report a preexisting nevus in the region of their newly diagnosed melanoma.

Nodular melanoma (NM) is the second most common melanoma variant, accounting for 15% to 30% of cases.[19] The majority of mucosal melanomas

are of the nodular variant. The lesion typically appears as a raised, blue-black or blue-red nodule. As hemangioma, blue nevus, pyogenic granuloma, and pigmented BCC can appear similarly, it is important to biopsy lesions with this appearance before treating them to avoid undertreatment.

As mentioned above, *LM* represents intraepidermal or melanoma in situ. Also known as “Hutchinson melanotic freckle,” it is often diagnosed in the background of chronic solar damage. The invasive counterpart to LM is *lentigo malignant melanoma (LMM)*. The exact percentage of LMs that progress to invasive LMM remains unknown.[50] It is speculated that if LM patients live long enough, all will progress to invasive melanoma. LM/LMM is commonly found within the H&N region. The subtype has been associated with older individuals, but the frequency in younger patients is increasing.[30] LM/LMM can display subepithelial extension as well as peripheral involvement with atypical junctional melanocytic hyperplasia (AJMH). These findings make achieving adequate surgical margins challenging from both an esthetic and a functional standpoint. Additional challenges associated with LMM are that both amelanotic and desmoplastic melanoma (DM) commonly arise in the setting of LM/LMM.

Desmoplastic Melanoma

DM is a rare subtype of melanoma composed of spindle cells with abundant collagen.[51] Although DMs are rare, accounting for only 1% of melanoma cases,[52] 75% are diagnosed in the HN region. They commonly arise in the setting of LMM. DMs are distinct from other melanoma subtypes in that they present in an older patient population; the median age of diagnosis is 61 years compared to 46 years.[52] Although amelanotic cases account for only 7% of cutaneous melanomas, up to 73% of DM and DNM have been found to be amelanotic.[52,53] This atypical appearance (Fig. 9.3), coupled with the spindle cell histology, makes DM somewhat of a diagnostic challenge. Immunohistochemistry (IHC) is helpful because the majority of tumors will stain positive for S100 and vimentin; HMB-45 is less reliable due to the amelanotic appearance. DM is highly infiltrative, has a propensity for neurotropic spread, and is considered locally aggressive. Spread along cranial nerves to the skull base and cavernous sinus is not uncommon. In addition, early local recurrences are reported as high as 49%, and this may be related to undetected perineural spread.[53]

Figure 9.3. Amelanotic melanoma of the nose mimicking basal cell carcinoma. Note the lack of traditional melanoma ABCD warning signs.

Primary treatment for DM remains surgical excision, with a minimum of 1 cm margins in order to prevent local recurrence. Pure DMs carry a low (<10%) rate of regional metastasis; therefore, sentinel lymph node biopsy (SLNB) is not recommended in this setting.[54] Despite the low rate of regional metastasis, patients with this diagnosis have a similar risk for the development of distant metastases as patients with NM of similar depth of invasion. More commonly, melanomas will be classified as "mixed" DM. These lesions carry the same rate of regional metastasis as do other melanoma subtypes, and SLNB should be offered to patients meeting the criteria outlined in Table 9.2. Evaluation of these lesions by an experienced dermatopathologist is critical in discerning between pure DM and mixed DM lesions.

Table 9.2 Indications for Cutaneous SLNB
Localized melanoma ≥1 mm depth of invasion (T1-T4N0)
Localized melanoma <1 mm depth of invasion (T1N0)
Demonstrating a poor prognostic feature include: Ulceration (T1bN0) Mitotic rate ≥1/mm^2 (T1bN0) Young age Angiolymphatic invasion Positive deep margin Tumor regression

Mucosal Melanoma

Mucosal melanoma (MM) represents a rare variant of melanoma, accounting for <2% of all cases.[55] Review of the Surveillance, Epidemiology, and End Results (SEER) database from 1987 to 2009 identified an increasing incidence of MM in the United States.[56] This increase was unique to the nasal cavity subsite, especially for women ages 55 to 84.

MM is regarded as a distinct and separate entity from its cutaneous counterpart. Unlike cutaneous melanoma, etiologic environmental factors have not been linked to the development of MM.[57] MM presents on average one decade later than cutaneous lesions.[58] In addition, women are diagnosed twice as often as men. Lastly, the BRAF oncogene mutation commonly identified in cutaneous melanoma is rarely found in the mucosal subtype. Instead, a relatively high incidence of KIT mutations has been reported.[59]

The majority of MMs arise in the nasal cavity. The anterior nasal septum is involved most often (33%), followed by the lateral nasal wall (28%), turbinates (15%), and nasal vestibule (10%).[60] The paranasal sinuses are another common site of origin, with the maxillary sinus involved most often. Given these anatomic locations, it is not uncommon for patients with sinonasal MM to present with nasal obstruction and epistaxis. These symptoms often lead to early diagnosis, with 75% of sinonasal patients presenting with localized disease only.[61]

Approximately 40% of HN MMs arise in the oral cavity (OC), with the upper alveolus and hard palate (Fig. 9.4) reported as the most common subsite (70%).[62] OC MM is often asymptomatic and can go undiagnosed until a neck mass develops from metastasis.[63] A review of five major MM series by Batsakis et al.[64] found laryngeal primary tumors to account for fewer than 4% of all cases. Within the larynx, the supraglottis was the most common site of origin.

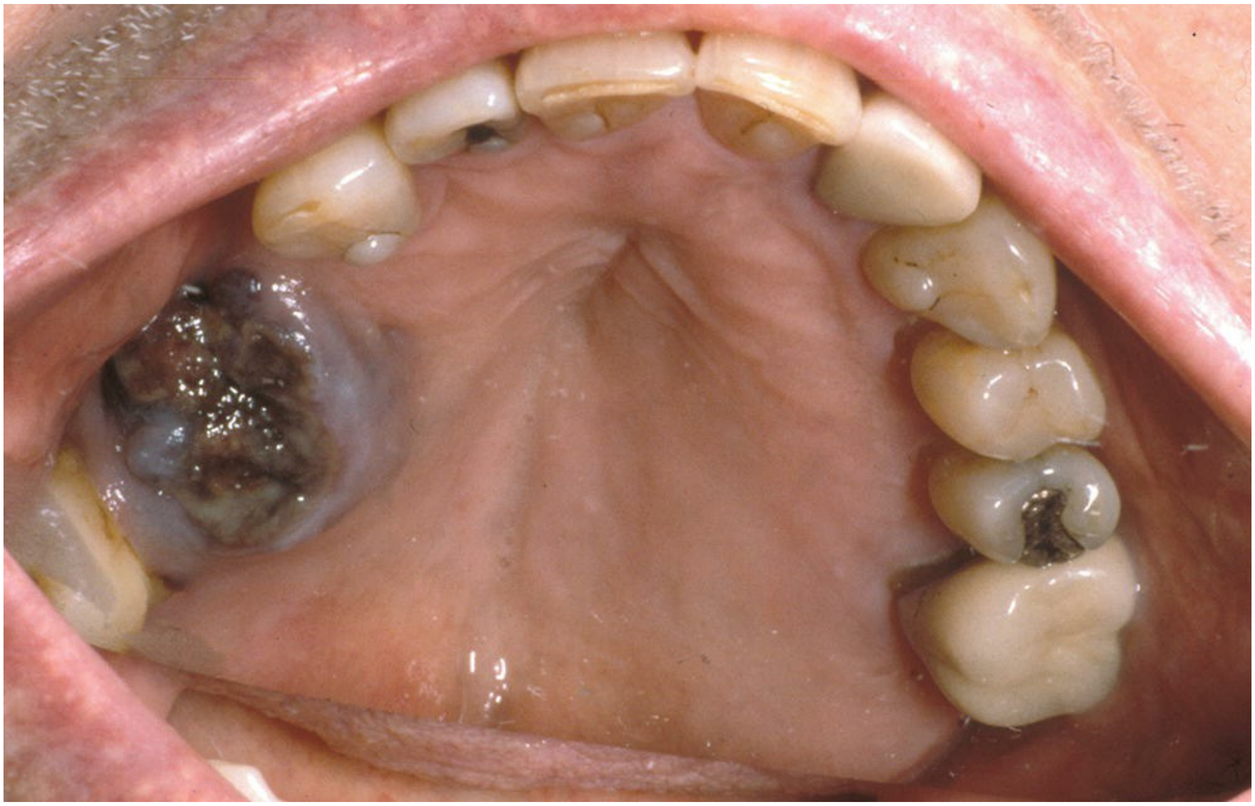

Figure 9.4. Mucosal melanoma of the hard palate. The oral cavity is the second most common site for mucosal melanoma, accounting for 40% of cases.

MM arises from respiratory stromal and mucosal melanocytes.[60] The diagnosis can be more challenging than that of cutaneous melanoma due to amelanotic nature of many tumors (Fig. 9.5). For this reason, IHC plays an important role in diagnosis. MM will often stain for S100, HMB-45, and Melan-A (MART1). Olfactory neuroblastoma may stain for S100 and HMB-45; however, the MAP-2, cytokeratin, and epithelial membrane antigen stains will facilitate the correct diagnosis.[65] Sinonasal undifferentiated carcinoma (SNUC) will stain for cytokeratin but not S100 or HMB-45. Lastly, plasmacytoma and lymphoma are routinely leukocyte common antigen positive in the absence of S100 staining.

Figure 9.5. Mucosal melanoma resected from the superior nasal cavity via a subfrontal craniotomy approach. Note the amelanotic nature of MM, which mimics a nasal polyp.

The recent 7th edition of the AJCC cancer staging system now incorporates a dedicated tumor–node–metastases (TNM) staging system for MM.[66] The staging system begins with stage III disease because of the overall poor prognosis of MM, even in the setting of limited primary tumor burden. Due to the overall aggressive nature of MM, T1 and T2 categories do not exist. T3 tumors are limited to the mucosa. T4a represents moderately advanced disease with invasion into the deep soft tissue, cartilage, bone, or overlying skin. T4b is reserved for very advanced disease, which includes the brain, dura, skull base, cranial nerve, masticator space, carotid artery, prevertebral space, and mediastinal structures. Regional disease and distant disease also impact patient outcome. Patients with nodal metastasis are classified as N1, which upstages them to stage IVA. Similarly, patients with distant metastasis are designated M1 and are classified as stage IVC.

Wide local excision (WLE) of the primary tumor remains the standard of care, and therapeutic neck dissection is recommended for known nodal metastasis.[57] Elective management of the N-zero neck is based upon the site of origin. Sinonasal MM is usually confined to the primary site at presentation.[67] For this reason, an elective neck dissection (END) is not typically recommended. However, OC MM carries an increased risk for

nodal metastasis and may warrant END.

Adjuvant radiation to the primary MM is recommended, regardless of depth of invasion. Extracapsular spread (ECS), two or more positive nodes, intraparotid nodal metastasis, any node >3 cm in diameter, and tumor recurrence are considered high-risk features warranting adjuvant radiation to the draining nodal basins.[57] Radiation planning is based on anatomic subsite and risk. The most common plan for high-risk MMs is conventional fractionation to 60 to 66 Gray (Gy) postoperatively or 70 Gy to gross disease.

Melanoma of the Auricle

Melanoma of the auricle was originally thought to carry a worse prognosis compared to other HN sites.[68] The increased risk was attributed to rich lymphatics, complex anatomic subdivisions of the auricle (6 hillock of His), and a paucity of subcutaneous tissue between the thin skin of the auricle and the underlying perichondrium.[69] For these reasons, total auriculectomy was historically considered standard of care. Retrospective reviews failed to demonstrate a difference in local recurrence based on the extent of auricular excision.[69] After accounting for known prognostic features such as tumor thickness, recent studies demonstrate similar survival rates between melanoma of the auricle compared to other anatomic sites.[70] It is now recognized that current prognostic indicators and surgical principles can be applied safely to the auricular region. Perichondrium is considered a barrier to the spread of melanoma.[71] For this reason, the underlying cartilage requires resection only in the setting of tumor involvement or if previous surgery/biopsy has violated the plane making it impossible for the surgeon to determine if there was direct tumor extension.

EVALUATION OF THE PATIENT

History

Approximately 25% of melanomas are diagnosed during routine office physical examination, whereas the vast majority of these cancers are first detected by the patient or his/her partner.[23,72] The earliest signs of melanoma include change in color, size, or shape of an existing lesion. The earliest

symptom is persistent pruritus. Bleeding, ulceration, and pain represent later changes concerning for more advanced disease. Patients should be questioned about a previous personal and family history of melanoma. Information elucidated during the history should include previous skin biopsies to include “mole” removal, sun exposure (history of blistering sunburns, tanning booth use, and occupation), and immunosuppression.

Physical Examination

Patients presenting with a suspicious lesion warrant a full body evaluation to include the skin as well as associated draining nodal basins. Ideally, this examination is performed by a physician who routinely treats patients with melanoma. A thorough physical examination is imperative because up to 8% of newly diagnosed patients have a synchronous cutaneous melanoma as well as a high risk of synchronous nonmelanoma skin cancers.[73]

In an effort to educate both physicians and patients on the warning signs of melanoma, the American Cancer Society (ACS) published the ABCD checklist.[74] Concerning signs include lesion Asymmetry, Border irregularity, Color variation within a lesion, or Diameter >6 mm. Although this ABCD checklist is helpful in identifying melanoma, it is not entirely comprehensive and will not detect every case of melanoma.[75] A subset of previously described cancers such as nodular, amelanotic (Fig. 9.3), and DMs lacks these common features of the ABCDs. For this reason, a seven-point checklist has been proposed in Europe, which focuses on the importance of *change* within an existing lesion.[76] In one series, 615 of 696 (88%) patients with melanoma recalled a change in their pigmented lesion prior to the diagnosis of melanoma.[77] This significance in a change with lesion led to the addition of “E”—evolving changes to the traditional ABCD warning signs.[78] Patients with melanoma will often present with significant solar damage and nevi. For this reason, a useful screening tool is also the “ugly duckling sign”[79,80] in which any pigmented lesion that appears significantly and individually different from surrounding lesions should be viewed with a high index of suspicion. This suspicion should remain high, even if the “ugly duckling” lesion lacks the traditional ABCDE warning signs.

Biopsy

Any pigmented lesion that demonstrates the ABCDE warning signs outlined above, has undergone change, or appears different from surrounding nevi warrants a biopsy with histologic evaluation. The differential diagnosis for cutaneous melanoma is quite broad, including seborrheic keratosis, hemangioma, blue nevus, Spitz nevus, pyogenic granuloma, pigmented BCC, and cutaneous SCC. It is important to view the biopsy of a melanotic lesion as a two-staged process: the first step involves histologic diagnosis including microstaging of tumor depth and evaluation of concerning features such as ulceration, mitotic rate, angiolymphatic invasion, and perineural spread. These results then serve as the guide for the second stage, which is definitive treatment with WLE and possible SLNB. Although combining the two steps by excising the lesion at the time of initial biopsy may seem both cost and time effective, clinical accuracy is uncertain. In addition, wide excision of the lesion may compromise the ability to accurately stage the melanoma with SLNB.[81]

If excisional biopsy is not feasible due to the large size or anatomic location of the concerning lesion, punch biopsy or incisional biopsy through the thickest portion of the neoplasm is recommended. Shave biopsy and fine needle aspiration of a pigmented lesion are discouraged because tumor thickness, which dictates further diagnostic workup as well as treatment, cannot be accurately determined. Both punch and incisional biopsies are subject to sampling error. If a diagnosis of melanoma is not rendered following either procedure, a repeat biopsy is suggested.

The American Academy of Dermatology (AAD)[82] and National Cancer Comprehensive Network (NCCN)[81] encourage standardization of reporting melanoma pathology. Dermatopathologists are encouraged to report tumor depth of invasion (measured in millimeters and often referred to as Breslow depth), mitotic rate, margin status (deep and peripheral), melanoma subtype to include pure desmoplasia if present, Clark histologic level of invasion for thin (≤1 mm) tumors, vertical growth pattern, tumor-infiltrating lymphocytes, tumor regression, and satellitosis.

Radiographic Imaging

Current NCCN staging guidelines[81] are outlined in Table 9.3. The majority of patients with melanoma present with localized lesions. They are usually

asymptomatic and lack clinical findings suggestive of regional or distant metastasis. Patients with melanoma in situ and stage IA disease (invasion up to 1 mm depth in the absence of ulceration, involvement beyond Clark level III, and high mitotic rate) are considered early stage, and imaging studies are not indicated.[83]

Table 9.3 National Comprehensive Cancer Network Workup Recommendations for Cutaneous Melanoma Based on American Joint Committee on Cancer Staging

Stage[66]	TNM	Recommendations
Stage 0	In situ melanoma	H&P only
Stage IA	T1aN0: depth ≤1 mm without ulceration or high MR	H&P only[a]
Stage IB	T1bN0: depth ≤1 mm with ulceration or high MR T2aN0: depth 1.01–2.0 mm without ulceration or MR	H&P SLNB
Stage II	T2bN0: depth 1.01–2.0 mm with ulceration or high MR T3aN0: depth 2.01–4 mm without ulceration or high MR T3bN0: depth 2.01–4.0 mm with ulceration or high MR T4aN0: depth >4.0 mm without ulceration or high MR T4bN0: depth >4.0 mm with ulceration or high MR	H&P SLNB
Stage III	Regional disease, satellite lesion, or in-transit metastasis	H&P FNA Baseline imaging
Stage IV	Distant metastasis	H&P FNA CT chest/abdomen/pelvis Brain MRI and/or PET

[a]SLNB can be considered in the setting of poor prognostic features outlined in Table 9.2.

TNM, tumor–nodal–metastasis staging description; H&P, history and physical examination; high MR, mitotic rate ≥1/mm^2; SLNB, sentinel lymph node biopsy; FNA, fine-needle aspiration of regional or distant disease; LDH, lactate dehydrogenase level; CT, computed tomography scan; MRI, magnetic resonance imaging; PET, positron emission tomography.

From National Cancer Comprehensive Network. NCCN clinical practice guidelines in oncology: melanoma. Available at http://www.nccn.org. Accessed April 14, 2014.

The most common site for distant metastasis is the lungs.[84] However, the incidence of occult pulmonary metastasis in an asymptomatic stage I and II disease is exceedingly low.[85] Routine chest radiograph (CXR) in this low-risk patient population carries a high false-positive rate of 7%,[86] necessitates additional evaluation, is not cost-effective, and is not suggested for stage I and II disease.[81,83] Evidence supporting the use of other screening modalities such as computed tomography (CT), liver–spleen scans, magnetic resonance

imaging (MRI), and bone scans for patients with limited stage I and II disease is lacking.[87] Site-specific imaging is only recommended in the event that a patient reports one of the symptoms listed in Table 9.4.[85] Routine blood tests are not recommended for stage I and II melanoma.[81] Screening lactate dehydrogenase (LDH) carries a 15% false-positive rate, does not correlate with SLN status, and has not been helpful in detecting occult disease in asymptomatic patients.[86] LDH is only recommended for stage I and II disease when the history or physical examination reveals jaundice, abdominal pain, or other specific findings raising concerns for distant metastasis.[85]

Table 9.4 Review of Systems to Guide Diagnostic Imaging Workup

Constitutional	Neurologic
Change in appetite/weight loss Fatigue and malaise Fever	Headache Memory loss Depression/mood changes Visual changes Seizures Loss of consciousness Numbness Weakness/paralysis
Respiratory	**Musculoskeletal**
Cough Hemoptysis Pleurisy/chest pain Dyspnea Recurrent pneumonia	Bone pain Joint pain
Hepatic	**Gastrointestinal**
Jaundice Abdominal pain Back pain	Abdominal pain Nausea/vomiting/anorexia Bleeding Constipation

Patients with stage III disease, who present with clinically or radiographically suspicious lymph nodes, satellite lesions, or in-transit lesions (defined by melanoma located >2 cm from the primary lesion), carry a significant risk of distant metastasis and warrant baseline imaging and FNA.[22,57] FNA is an accurate and cost-effective means to confirm metastatic melanoma.[88]

Patients with known stage IV disseminated melanoma required a comprehensive workup for systemic metastasis. Clinical trial protocols often dictate the evaluation in this setting.[22] The NCCN recommends FNA, if feasible, to confirm the distant metastasis disease as well as LDH testing.[81] A survival benefit has not been found between patients who are asymptomatic when diagnosed with distant stage IV disease compared to their counterparts who are diagnosed with symptomatic stage IV disease.[85] Although a thorough evaluation for systemic metastasis will not impact overall survival, it may lead to improvement in the patient's quality of life.

Sentinel Lymph Node Biopsy

Because multiple prospective, randomized trials failed to demonstrate an overall survival benefit for patients undergoing END,[89–93] the NCCN no longer suggests routine END for melanoma.[81] The procedure has been replaced by SLNB, which is a much less invasive, cost-effective, and efficient means of staging and screening patients for regional metastasis.[94] Cross-sectional imaging using traditional radiographic modalities only identifies 0.5% to 3.7% of occult stage III melanoma cases.[95–98] Given the often minute tumor volume in a positive sentinel node (+SLN), serial sectioning and evaluation with both H&E staining and IHC for melanoma markers confer greater sensitivity in the detection of micrometastasis disease and are recommended for all sentinel nodes found to be negative for melanoma on conventional H&E staining and microscopic examination.

Patients meeting the criteria outlined in Table 9.2 should be counseled on the utility of SLNB. Approximately 4 to 6 hours prior to surgery, patients undergo preoperative injection of a radioactive colloid into the lesion and lymphoscintigraphy to determine the number, location, and laterality of at-risk draining nodal basins (Fig. 9.6). This imaging serves as a road map for the surgeon and is particularly helpful for midline lesions, which have the

propensity to drain bilaterally. Recent studies demonstrate that fused single-photon emission computed tomography/computed tomography (SPECT/CT) is a superior imaging modality compared to traditional planar lymphoscintigraphy because of the increased anatomical three-dimensional detail and improved resolution (Fig. 9.7). The largest prospective study comparing SPECT/CT to planar lymphoscintigraphy included 403 melanoma patients.[99] SPECT/CT altered the surgical plan in 22% of cases. It yielded a higher number of + SLNs per patient (2.4 vs. 1.87; $p < 0.001$) as well as a higher metastatic rate (0.34 vs. 0.21; $p = 0.04$). At a mean follow-up of 28.8 months, patients undergoing SLNB utilizing SPECT/CT had a higher disease-free survival (DFS) compared to the lymphoscintigraphy group (94% vs. 79%; $p = 0.02$). Multivariate analysis identified use of SPECT/CT as a factor associated with DFS (HR = 4.11; $p = 0.02$).

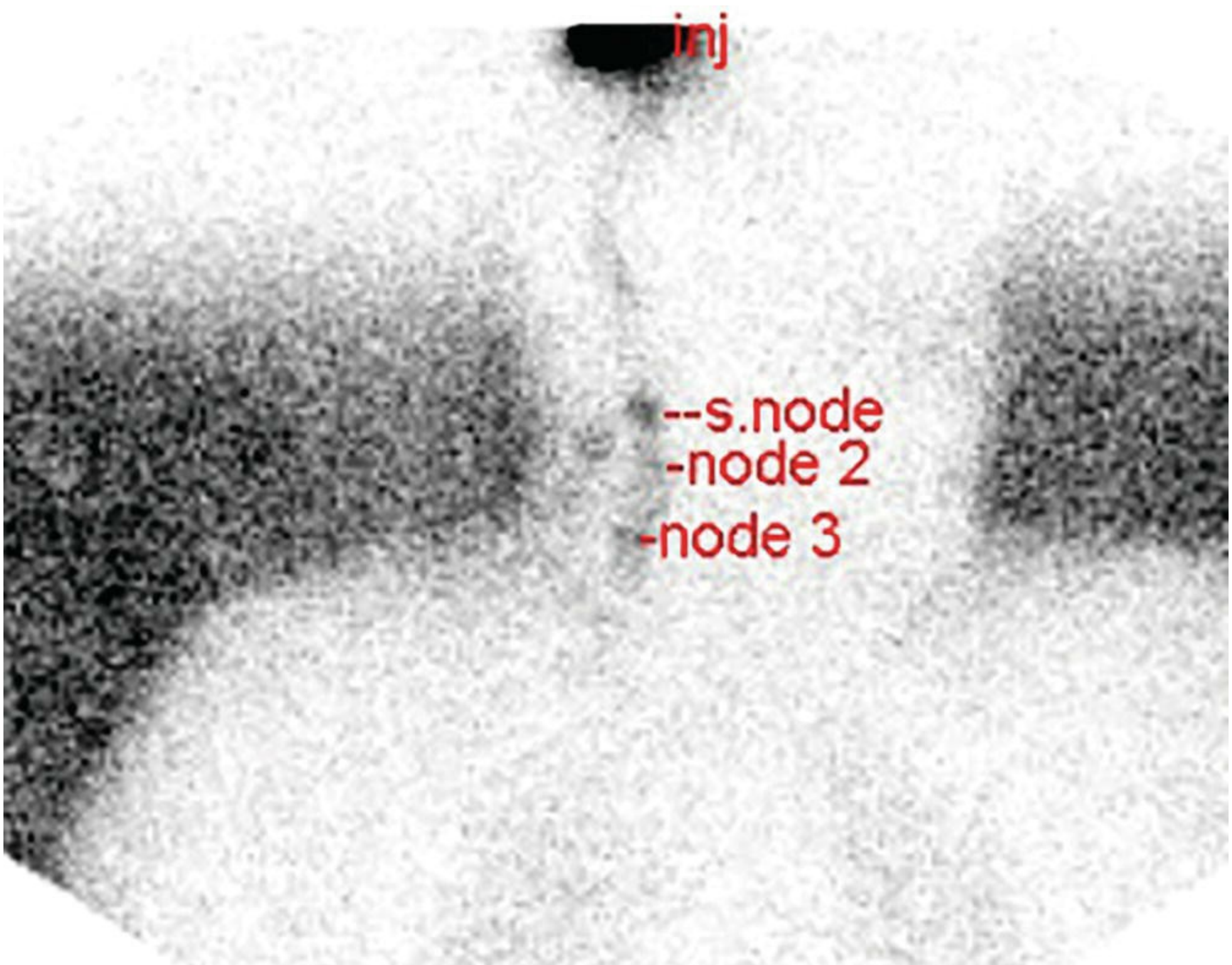

Figure 9.6. Sentinel lymph node biopsy traditional two-planar imaging

utilizing preoperative radioactive colloid and lymphoscintigraphy. The hottest region represents the primary right scalp melanoma where intradermal injections were performed (inj site). S. node, sentinel node.

Figure 9.7. Sentinel lymph node biopsy SPECT/CT fused coronal imaging of

a patient with a left scalp melanoma (*white circle*). A sentinel lymph node with radiolabel uptake is detected in the left parotid nodal basin. Note increased anatomic detail compared to lymphoscintigraphy in Figure 9.6.

Once under anesthesia, patients undergo intraoperative lymphatic mapping with vital blue dye.[100] Approximately 1 mL of dye is injected intradermally into the four quadrants surrounding the primary melanoma. Combining both the radioactive colloid and blue dye is highly recommended because studies consistently demonstrate increased SLNB sensitivity when using both techniques together.[101,102]

WLE of the HN primary is often performed first because the close proximity of the melanoma and draining lymphatics creates radioactive "shine-through" that can make the gamma probe readings difficult to interpret in certain basins underlying or very close to the primary melanoma. Following WLE, the nodal basins at risk based in part on the preoperative lymphoscintigraphy are evaluated for increased radioactivity using a handheld gamma probe (Fig. 9.8). The smallest incision possible to remove the SLN without risk to neurovascular structures is then made overlying the areas of increased radioactivity. Approximately 25% of HN cutaneous melanomas drain to the parotid nodal basin.[103,104] A preauricular incision is recommended in the parotid region in order to optimize cosmesis and minimize injury to the facial nerve (Fig. 9.9). The use of facial nerve monitoring can also decrease the risk of facial nerve injury. Numerous studies demonstrate that SLNB can be reliably and safely performed within the parotid nodal basin, especially when using continuous facial nerve monitoring.[104–106] It had previously been thought that inflammation from the biopsy would increase the risk of facial nerve injury when a therapeutic superficial parotidectomy was required for patients with a + SLN.[107] However, Erman et al.[108] reported preservation of facial nerve function in all patients undergoing therapeutic superficial parotidectomy following a positive SLNB.

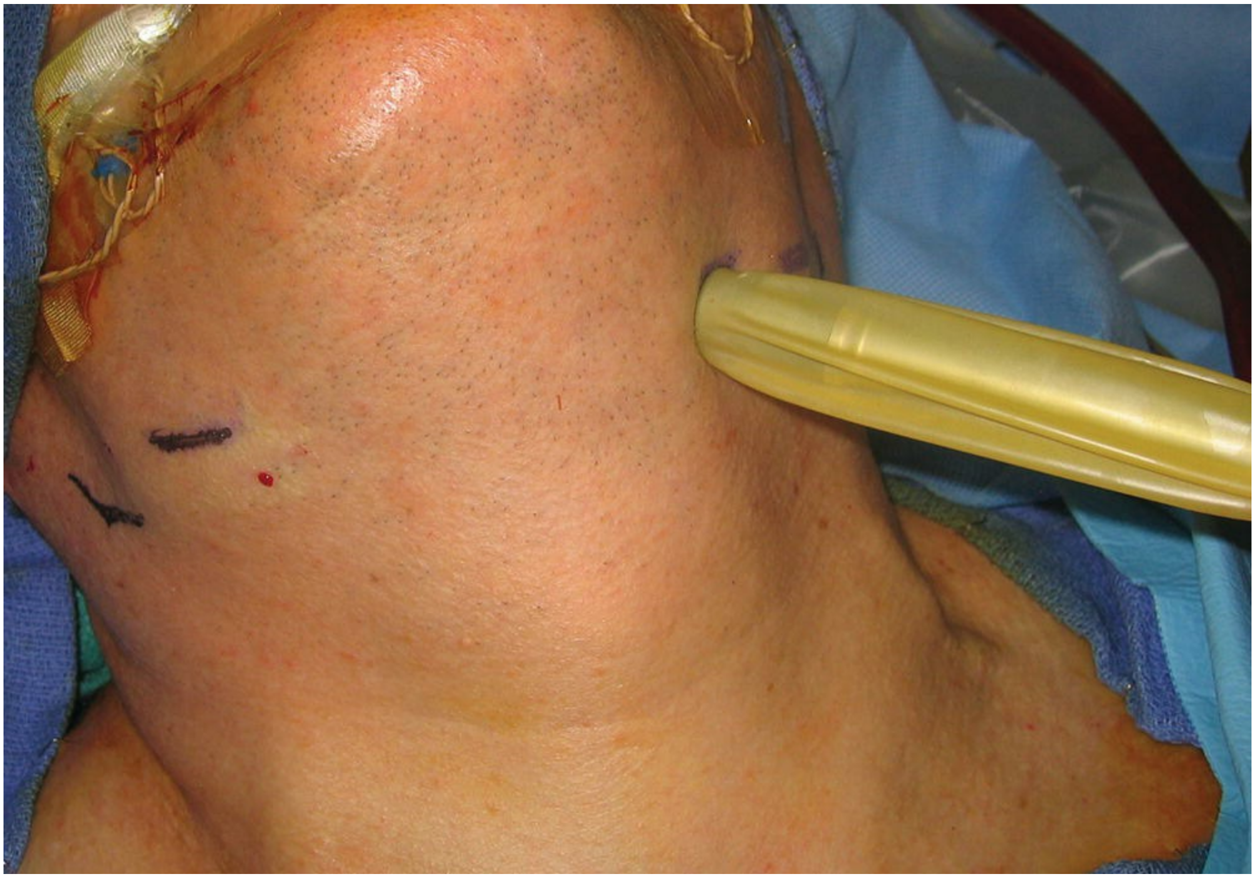

Figure 9.8. Following preoperative injection of radioactive colloid, intraoperative injection of blue dye, and wide local excision of the primary melanoma, the gamma probe is utilized to identify increased areas of radioactivity indicative of a sentinel node.

Figure 9.9. A preauricular incision and facial nerve monitor is sometimes recommended for SLNB within the parotid nodal basin to allow for optimal cosmetic healing and reduced risk to the facial nerve, respectively.

By definition, a lymph node demonstrating 10% or greater counters per minute compared to the hottest node ex vivo is considered “sentinel”[109] Using a combination of the gamma probe and visual cues from the blue dye, individual SLNs are identified (Fig. 9.10) and sent separately for permanent histologic evaluation because frozen section evaluation of melanoma specimens has a false-negative rate between 5% and 10%.[110] The evaluation includes serial microsectioning, hematoxylin and eosin (H&E) staining, and melanoma-specific immunohistochemistry to include S100, Melan-A (MART1), and HMB-45. On average, 2.4 SLNs are harvested per patient.[108] This small number allows for a more practical, thorough, and complete histologic evaluation compared to an entire lymphadenectomy specimen, which can yield too many lymph nodes to cost-effectively evaluate with more

than a single H&E section.[111] Patients with a + SLN should be returned to the operating room within 2 weeks of diagnosis for definitive therapeutic lymph node dissection (TLND); patients with a negative biopsy are followed clinically.

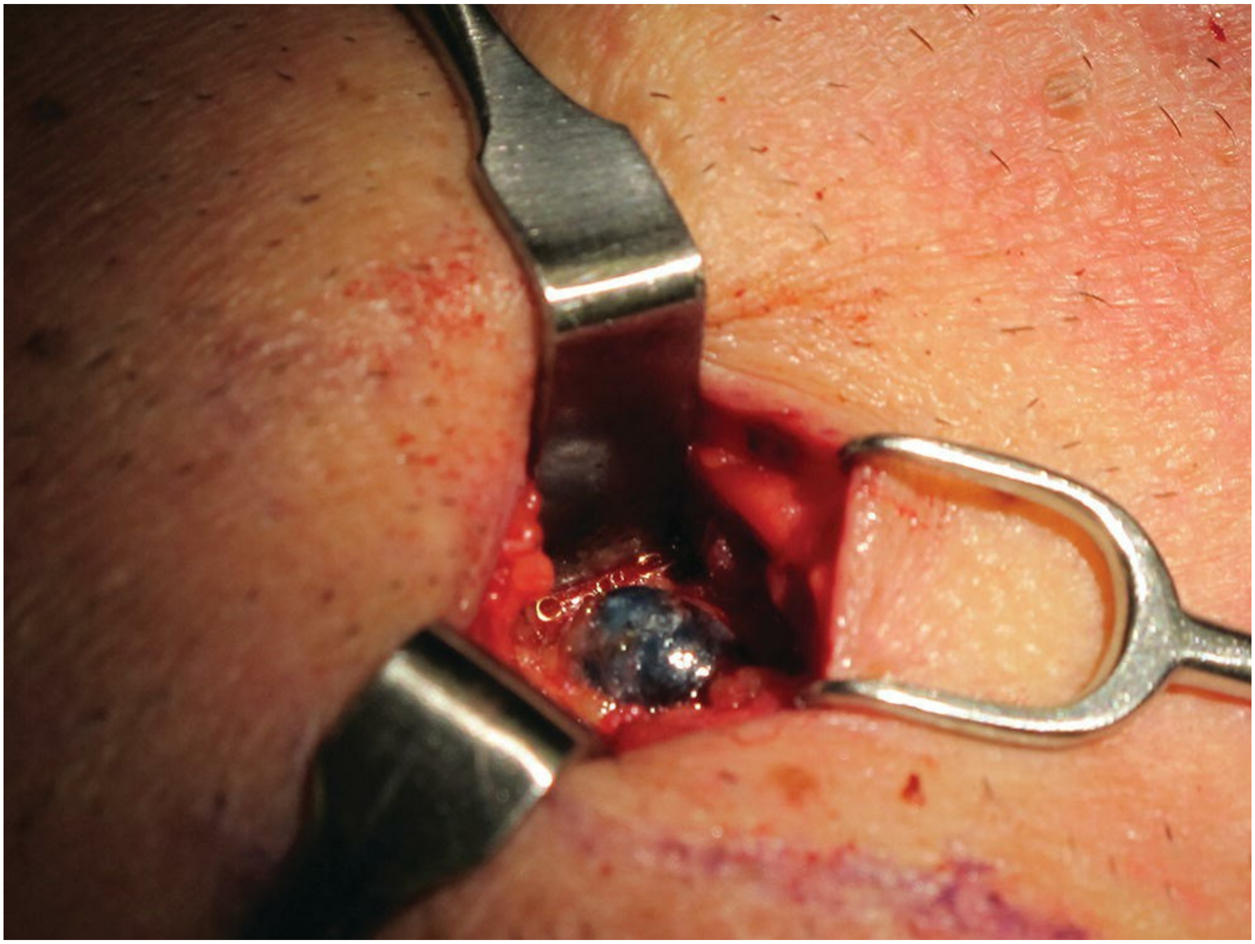

Figure 9.10. A sentinel lymph node identified by increased radioactivity and demonstrating the expected intense staining from the intradermal injection of the primary lesion with blue dye.

END no longer has a role in cutaneous melanoma,[57] and SLNB is now considered standard of care for the reasons outlined in Table 9.5.[119,120] Although damage to cranial nerves and unpredictable lymphatics were an original concern in applying SLNB within the HN region,[107] studies throughout the past two decades have consistently demonstrated that SLNB can be accurately performed in cervical nodal basins without significant risk to the cranial nerves and great vessels.[104,121–123] The largest single-institution

HN SLNB prospective study identified an SLN in 352 of 353 cases (99.7%) with no reported permanent facial nerve, cranial nerve, or vascular damage. Sixty-nine of 353 patients (19.6%) had a positive SLN biopsy.[108] This 19.6% positivity rate mirrors the results achieved in other anatomic sites such as the trunk and extremities.[92,124] At a mean follow-up of 48 months, 12 of 283 negative SLN patients were locally free of disease but developed regional recurrence within a previously mapped nodal basin, yielding a false-negative rate of 14.8% (12 false-negatives/12 false-negatives + 69 true positives). The negative predictive value of 95.8% and false rate of omission of 4.2% mirror that of trunk and extremity melanoma, thus demonstrating feasibility of SLNB in the HN region.

Table 9.5 Supporting Rationale for SLNB as Standard of Care for Cutaneous Melanoma

1. The pathologic status of the SLN is the most important prognostic factor for melanoma disease free survival (HR = 3.41; $p < 0.00001$) and overall survival (HR = 6.53; $p < 0.0001$).[112]
2. Lymph node tumor burden (microscopic/occult disease vs. macroscopic/clinically palpable disease) is the second most important prognostic factor following number of nodal metastasis for patient with stage III melanoma ($p < 0.0001$).[113]
3. The *American Joint Committee on Cancer (AJCC)* incorporated SLN status into the 2002 cancer staging system[114] and has validated the prognostic importance of the SLN status in the most recent edition.[115]
4. SLNB remains the most specific and sensitive means for regional staging.[81]
5. SLNB allows for accurate staging and identification of a homogeneous population of patients to enroll in clinical trials.[116]
6. SLNB is now incorporated into the current *National Comprehensive Cancer Network (NCCN)* guidelines.[81]
7. The *American Society of Clinical Oncology (ASCO)* and the *Society of Surgical Oncology (SSO)* have recently published updated clinical practice guidelines regarding use of SLNB for melanoma.[117]
8. *The World Health Organization (WHO)* issued a statement that SLNB is standard of care for melanoma.[118]
9. SLNB is incorporated into numerous national and international numerous oncology consensus statements.[82,119,120]

Communication and collaboration are imperative to SLNB success. An experienced nuclear medicine team is necessary to avoid inappropriate administration of the radioactive tracer causing "shine-through." The pathologist plays an extremely critical role given the tedious task of identifying micrometastasis, which can measure <1 mm in size.[125] The referring dermatology team is vital in working up and identifying appropriate SLNB candidates. Lastly, the surgeon requires experience in the SLNB technique. Morton et al.[110] prospectively identified a 55-case learning curve in order to achieve at least 95% accuracy with SLNB.

In 2014, SLNB remains a staging modality. The long-awaited multicenter selective lymphadenectomy trial-1 (MSLT-1) led by Donald Morton commenced in 1994 to determine if immediate completion lymphadenectomy improved survival over observation and delayed lymphadenectomy.[126] A total of 2001 patients with melanoma were randomized to WLE and delayed lymphadenectomy for nodal recurrence versus WLE with SLNB and immediate lymphadenectomy for micrometastatic disease. At 10-year follow-up, SLNB correctly determined the pathologic nodal stage in 96% of cases. Patients with a + SLN demonstrated worse outcomes compared to their SLN-negative counterparts (DFS 62% vs. 85%; $p < 0.001$). Intermediate and thick melanoma patients in the WLE/SLN group experienced an improved 10-year DFS compared to observation with delayed lymphadenectomy. Although an overall survival benefit was not reported for the entire 2001 cohort, only 20% were estimated to harbor occult nodal metastasis and benefit from early intervention. Subgroup analysis of patients with nodal disease identified an improved melanoma-specific survival in the WLE/SLN group (62% vs. 41.5%; $p = 0.006$). This treatment-related difference was unique to patients with intermediate-thickness melanomas (1.20 to 3.5 mm) but not thick melanomas >3.5 mm in depth. The final MSLT-1 results demonstrate that early lymphadenectomy following a + SLNB decreases nodal recurrence, distant metastasis, and death from melanoma for patients with intermediate-thickness melanomas and occult regional disease.

The benefit of SLNB in staging thin melanomas remains to be determined. Morton et al.[126] could not draw meaningful conclusions from the 340 patients with thin melanomas measuring <1.20 mm invasion. A meta-analysis of SLN positivity in thin melanomas ≤1 mm identifies a pooled occult nodal disease rate of only 5.6%.[127] Clinical and histopathologic

criteria to reliably detect this small at-risk population has not emerged. Future studies are required and will need to balance benefit with cost and associated morbidity. Table 9.2 lists situations in which SLNB can be considered in the setting of thin melanomas.

Future SLNB research endeavors hold exciting promise. Ongoing efforts investigate the *therapeutic potential* of SLNB. Studies have attempted to identify markers of both the primary melanoma and SLN predictive of cancer remaining in non-SLNs.[128–130] Such markers would allow for identification of the subset of + SLN patients who may not require further completion TLND. Unfortunately, a reliable marker has yet to emerge. The ongoing *MSLT-II trial* is designed to investigate the indications for TLND following a + SLNB.[110] It will determine if immediate TLND provides a survival benefit over postoperative, diligent, ultrasonographic monitoring of the draining nodal basins. Until the results of MSLT-II are available, it is important to realize that TLND following + SLNB remains the standard of care.[81] SLNB implementing *optical imaging* with near-infrared fluorescence utilizing indocyanine green (NIR-ICG) as a lymphatic tracer has been successfully applied in various cancers.[131] NIR fluorescence has outperformed traditional blue dye in several SLN clinical trials.[132–135] Tissue depth and large body mass index (BMI) remains the rate-limiting factor. A hybrid tracer combining ICG with ^{99m}Tc-radioactive colloid has been introduced in an attempt to increase depth of detection and length of time the tracer is retained within the lymph nodes.[136] The application of SLN optical imaging remains investigational at present but is promising.

STAGING AND PROGNOSIS

As a result of an increased understanding of the biology of cutaneous melanoma, the AJCC introduced a revised staging system in 2009.[115] The sample size was expanded to 17,600 patients, the prognostic significance of mitotic rate was analyzed, the stage IV category was expanded fivefold, LDH levels were formally evaluated for the first time, and the importance of SLN status as criterion for stage III disease was evaluated. This investigation marks the largest analysis of its kind to date.

The current AJCC staging system for cutaneous melanoma remains

founded upon the traditional TNM classification system.[115] Stages I and II represent localized disease, stage III is regional disease inclusive of satellite and in-transit metastasis, and stage IV is reserved for distant metastatic disease. The most important predictors for survival now serve as criteria for the definition of melanoma stage and are summarized in Table 9.6.

Table 9.6 AJCC Cutaneous Melanoma Staging Criteria Defining Tumor Stage

Stage I and II: Localized Disease 1. Tumor thickness (recorded in even integer increments) 2. Tumor ulceration 3. Mitotic rate for thin T1 melanomas (≤1 mm thickness)
Stage III: Regional Metastasis 1. Number of metastatic lymph nodes 2. Tumor burden (microscopic + SLN vs. macroscopic) 3. Primary tumor ulceration 4. In-transit or satellite metastasis
Stage IV: Distant Metastasis 1. Site of distant disease 2. LDH level

+ SLN, positive sentinel lymph node; LDH, serum lactate dehydrogenase level

From American Joint Committee on Cancer (AJCC). *Staging Manual*. Chicago, IL: Springer Science and Business Media, LLC; 2010.Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Multivariate analysis of 13,500 patients with localized disease confirmed tumor thickness and ulcerations as the most important predictors of outcome.[115] Overall, *tumor thickness* remained the most important risk factor for stage I/II patients. It was previously incorporated into the 1997 staging system, but at that time, it was empirically based on the Breslow depth.

Recent analysis confirmed that even integer cut points (1.0, 2.0, 4.0 mm) represent the best statistical model correlating thickness and survival. Ten-year survival rates were reported as 92%, 80%, 63%, and 50% for T1 through T4 tumors, respectively.[115]

Primary tumor *ulceration* was identified as the second most important factor for localized stage I/II disease. It is a histologic diagnosis in which the epithelium overlying the primary tumor is absent. Patients with ulcerated melanomas carry a worse survival rate, mirroring that of patients with nonulcerated tumors in the next higher T-category.[114]

Primary tumor *mitotic rate* is now incorporated into the staging of the thinnest T1 melanomas. Mitotic rate is an indicator of tumor proliferation and is reported in features per mm^2. Increased mitotic rate is associated with a worse survival rate,[115] and it is recognized as an independent predictor of a positive SLN[137,138] as well as the second most powerful predictor of survival for patients with stage III + SLN disease. Multivariate analysis of 10,233 patients with localized stage I/II disease found mitotic rate to be the second most powerful predictor of overall survival following tumor thickness ($p < 0.0001$).[115] Mitotic rate has now replaced Clark level of invasion for thin T1 melanomas; when this is present, patients are staged as T1b.

Stage III melanoma is a heterogeneous group of patients with a 5-year survival rate ranging from 82% for patients with nonulcerated primaries with 1 + SLN to a dismal 29% for patients with ulcerated melanomas with ≥4 clinically palpable metastatic nodes.[115,139] The heterogenous survival rate for stage III melanoma highlights the importance of accurate tumor staging, which is particularly important in the context of clinical trials.[116] The *number of nodal metastasis* remains the most important prognostic factor for stage III disease, regardless of micrometastatic versus macrometastatic deposits. Other important prognostic factors include tumor burden (micrometastatic disease identified on SLNB vs. clinically palpable macroscopic disease); the majority of stage III melanoma patients now present with micrometastasis.[140] Ulceration remains the only prognostic factor of the primary lesion once patients develop regional disease; tumor thickness is no longer prognostic once patients develop regional metastasis. *In-transit metastases* and *satellite lesions* represent intralymphatic metastasis and are considered stage III disease, even in the absence of nodal metastasis.

Stage IV melanoma describes patients with distant metastasis. Analysis of 7,972 patients with disseminated melanoma confirmed anatomic site and elevated serum LDH levels as the most important prognostic factors.[115] Patients with distant metastasis to the skin, subcutaneous tissue, or distant lymph nodes with a normal LDH level (M1a) had a slightly higher survival rate as compared to other subsites. Patients with only lung metastasis have a better prognosis than those with involvement of other visceral distant metastasis and are denoted as having stage M1b disease. Patients with metastasis involving any other visceral organs and those with elevated LDH levels (regardless of the site of metastatic disease) have the worst prognosis and are categorized as M1c. The median survival time following the diagnosis of disseminated melanoma is only 6 to 8 months; the 5-year survival rate is 6%.[141,142] For this reason, stage IV melanoma is not subclassified under the AJCC staging system.

The AJCC has now incorporated staging guidelines for metastatic disease with unknown primary origin.[115] Patients with isolated nodal metastasis are considered stage III, provided that a comprehensive workup does not find evidence of distant disease. All other presentations of metastatic melanoma with unknown primary are deemed stage IV disease. Patients with unknown primary melanoma carry an equivalent to better outcome compared to those with a known primary in the same staging category.[143,144]

SURGICAL MANAGEMENT

Primary Melanoma

WLE remains the primary treatment for cutaneous melanoma. The extent of surgical margins remains an unanswered question despite numerous retrospective studies, meta-analyses, and clinical trials. Numerous prospective trials[145–148] investigating the optimal surgical margin for intermediate-thickness melanomas failed to demonstrate improved local control rates and overall survival in using margins >1 cm. Meta-analysis of such trials concluded that a surgical margin of at least 1 cm and no more than 2 cm was adequate for WLE.[149] Current surgical margins are dictated by melanoma depth of invasion (Table 9.7).[81] The depth of excision includes full-thickness skin and subcutaneous tissue. Resection of fascia,

perichondrium, and periosteum is required only in the setting of direct tumor invasion or if the surgical plane was violated during a previous biopsy.[150] These recommendations serve merely as a guideline; each patient must be treated on an individual basis, with surgeon experience and judgment playing an important role.

Table 9.7 Recommended Surgical Margins for Cutaneous Melanoma WLE

Tumor Depth	Surgical Margin
In situ	0.5–1.0 cm
≤1 mm (T1)	1.0 cm
1.01–2.0 mm (T2)	1.0–2.0 cm
2.01–4.0 mm (T3)	2.0 cm
>4.0 mm (T4)	2.0 cm

From National Cancer Comprehensive Network. NCCN clinical practice guidelines in oncology: melanoma. Available at http://www.nccn.org. Accessed April 14, 2014.

Wide undermining allows for the closure of the majority of HN melanoma defects. Larger defects may require reconstruction with a skin graft, advancement flap, regional flap, or free tissue transfer. A delay in closure may be required until the surgical margins are adequately cleared on permanent pathology. Rush permanent section analysis of margins is available in many centers enabling patients to have delayed reconstructions performed within 24 hours of the initial primary resection. The method of reconstruction ultimately depends on the anatomic location including skin color and texture, depth of the defect, and patient, as well as surgeon, preference. The method of closure has not been shown to hinder detection of melanoma recurrence or to negatively impact survival.[151]

LM/LMM can be a challenge to excise due to the propensity for unpredictable, subclinical spread involving AJMH.[152] Positive margins are not uncommon. Application of a Wood lamp or digital epiluminescence

microscopy has proven helpful in the accurate identification of tumor margins.[152] A prospective trial of 1,120 LM patients treated with MOHS microsurgery yielded removal of 99% of melanomas using a 9-mm margin and 86% with a 6-mm margin.[153] Alternatively, the “square” technique[154,155] is a staged procedure in which a double-bladed instrument is used to completely excise the peripheral margins. This technique allows permanent histologic evaluation of 100% of the peripheral margins surrounding the entire melanoma. On rare occasions, WLE of large LM/LMM is not feasible due to the associated comorbidities and psychosocial implications. Topical imiquimod[156] and primary radiation[157,158] are reasonable alternatives in these challenging cases.

Regional Lymph Nodes

The cervical and parotid nodal basins are the most common site of metastasis for HN cutaneous melanoma.[7,140,141] TLND is universally accepted as the standard of care for regional nodal disease.[81] The neck dissection must surgically address the draining nodal basins as well as the intervening lymphatics between the primary melanoma and the site of known regional disease. Every effort should be made to preserve the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle.[142] These structures should only be sacrificed when there is guidance of gross tumor invasion.

The location of the primary melanoma dictates the type of TLND, as well as the need for a superficial parotidectomy (Fig. 9.11). An imaginary coronal plane through the external auditory canal (EAC) serves as a guide: melanomas located anterior to this plane (i.e., anterolateral scalp, temple, lateral forehead, lateral cheek, and ear) drain via the parotid nodal basin to the jugular lymph node chain.[142] Adequate management of the nodal basins for these melanomas located anteriorly and superiorly in the HN region requires both a superficial parotidectomy and a modified radical neck dissection (MRND). If the melanoma arises anterior to the imaginary coronal plane through the EAC, but in a more inferior location (i.e., chin or neck), a superficial parotidectomy is not warranted. Conversely, melanomas located on the scalp and occiput, posterior to the imaginary coronal plane through the EAC, can drain to postauricular, suboccipital, and posterior triangle lymph nodes. These nodal basins are not addressed during routine MRND. Instead, a posterolateral neck dissection, which extends to the midline of the superior,

posterior neck, is required.[143]

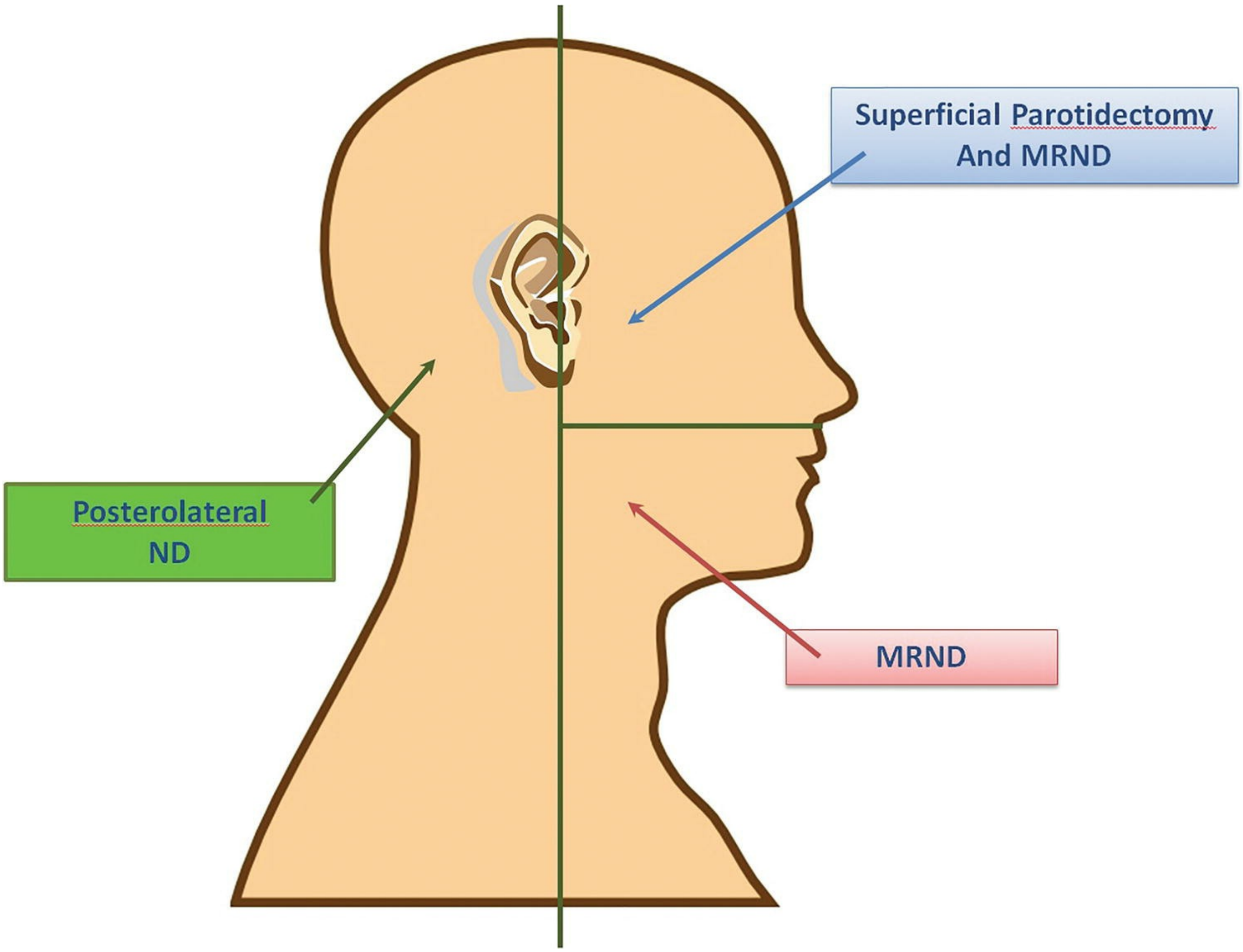

Figure 9.11. The type of neck dissection and need for superficial parotidectomy are dictated by the location of the primary melanoma.

In-Transit Metastasis

WLE of in-transit metastasis remains the standard of care when clear margins can be achieved.[81] Ultimately, the treatment will be based upon the size of the in-transit metastasis, anatomic location, number of metastatic lesions, and overall patient prognosis. Patients with in-transit stage III disease are at increased risk for occult regional metastasis, and a + SLNB in this setting portends a worse prognosis.[159] Nonsurgical options include intralesional injections with bacille Calmette-Guerin (BCG),[160] interleukin-2 (IL-2), interferon, laser ablation, and topical imiquimod.[161] Consensus has not been reached for the optimal nonsurgical treatment of in-transit melanoma

metastasis; enrollment into clinical trials is encouraged for this patient population.[81]

Distant Metastasis

Patients with stage IV melanoma metastasis to distant sites have an exceedingly grave prognosis with an overall survival rate measured in months as opposed to years. Surgical intervention is reserved for palliation in patients suffering from brain, lung, gastrointestinal, subcutaneous soft tissue, and distant lymph node metastasis.[162] Surgery should only be considered if clearly identifiable and specific symptoms are associated with the metastatic lesion. Consideration must be given to surgical morbidity, expected quality of life, anticipated survival, and, most importantly, patient's wishes.[22] The patient and family must understand that the goal of each surgery is palliative in nature.

RADIATION

Although surgery offers the highest rate of local control and cure, radiation can have a role as the primary treatment modality for elderly individuals who are deemed poor surgical candidates. Radiation may also be considered the primary treatment modality for patients with exceedingly large melanomas (usually of the LMM variant) in which WLE would be extremely morbid from a cosmetic and functional standpoint.[158]

Radiation is most often used in the setting of adjuvant treatment following WLE and/or regional lymphadenectomy. The rationale for adjuvant radiation is to improve local and regional control rates without adding toxicity. Preventing regional recurrence is important given the associated morbidity and negative impact on quality of life. Indications for adjuvant radiation to the primary surgical bed and regional nodal basis are outlined in Table 9.8. Hypofractionation (3 fractions of 7 Gy administered days 1, 7, and 21 or 5 to 6 Gy fractions) is the most common regimen.[81,163,164] Patients meeting the criteria listed in Table 9.8 are often eligible to receive adjuvant interferon-α2b (see below). Interferon is thought to act as a radiosensitizer; adjuvant radiation is usually delayed until the 4-week induction phase of interferon therapy is complete.[165]

Table 9.8 Indications for Adjuvant Cutaneous Melanoma Irradiation

Local Irradiation	Regional Irradiation
Desmoplastic melanoma	≥1 Parotid node
Positive margin	≥2 Cervical nodes
Recurrent disease	Cervical node ≥3 cm diameter
Breslow depth >4.0 mm with ulceration	Extracapsular spread
Satellitosis	+ SLN without completion lymphadenectomy
	Regional metastasis

Adapted from National Cancer Comprehensive Network. NCCN clinical practice guidelines in oncology: melanoma. Available at http://www.nccn.org. Accessed April 14, 2014;

Rao NG, Yu HH, Trotti A III, et al. The role of radiation therapy in the management of cutaneous melanoma. *Surg Oncol Clin North Am.* 2011;20:115–131;

and Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol.* 2012;13:589–597.

Guadagnolo et al. reported a statistically significant improvement in 5-year regional control rates for HN patients undergoing cervical TLND followed by adjuvant irradiation versus cervical TLND alone (43% vs. 93%; $p < 0.001$).[164] Burmeister et al.[166] conducted a prospective trial in which patients were randomized following lymphadenectomy to adjuvant radiation versus observation. At 40 months' follow-up, no difference in disease-specific and overall survival was reported. However, the improved regional control rate (HR = 0.56; $p = 0.041$) compelled the authors to conclude that radiation improves regional control in patients at high risk for nodal relapse following lymphadenectomy.

Radiation can also play a role in the palliative setting.[163] Hypofractionated dosing is suggested in order to limit toxicity as well as the

amount of time spent in treatment. Individual lesions are usually treated only after becoming symptomatic. The exception is brain metastases, which tend to be irradiated preemptively in order to prevent cerebral hemorrhage.[163] As with all palliative care, the focus ultimately is one of quality as opposed to quantity of life.

SYSTEMIC THERAPY

Chemotherapy and Biologic Agents

Melanoma is a relatively chemoresistant tumor, and a definite impact of treatment with conventional chemotherapy on overall survival has not emerged.[167] Consequently, the main role of chemotherapy remains in palliative treatment for metastatic stage IV disease.[81] *Dacarbazine (DTIC)* was the first chemotherapeutic agent to show significant activity against melanoma, and today, it remains the only agent approved for chemotherapeutic agent for treating stage IV melanoma. Unfortunately, chemotherapy response rates are between 10% and 20%, with <5% demonstrating a complete response.[168–170] This modest response has led to increased focus on targeted therapies outlined below.

IL-2 is a variant of immunotherapy used as the primary treatment for disseminated stage IV metastatic melanoma. IL-2 stimulates the immune host response by activating natural killer cells (NKCs), monocytes, cytotoxic T cells, and helper T cells. Initial trials involving high doses of IL-2 were promising with an overall response rate of 7% and partial response rate of 10%, both of which were long-standing between 8 and 10 years.[171] IL-2 toxicities are significant and can be life threatening. Only patients with outstanding performance and cardiopulmonary status are eligible for clinical trials.[22] Various randomized trials have combined IL-2 and other biologic agents with various chemotherapy drugs, including DTIC, cisplatin, and vinblastine.[172,173] Although these biochemotherapy regimes demonstrate overall response rates, a survival benefit for patients with metastatic melanoma has not been reported.[174]

Interferon-α2b

Despite myriad clinical trials involving adjuvant regimens, high-dose interferon-α2b (INF-α2b) remains the *only US Food and Drug Administration (FDA)-approved adjuvant treatment for stage III melanoma*. Three large clinical trials involving adjuvant INF-α2b have been conducted by the Eastern Cooperative Oncology Group (ECOG).[175–177] ECOG trial E1684 was the first study to demonstrate the efficacy of INF-α2b.[175] High-dose interferon was administered intravenously during a 1-month induction period (20 million units[MU]/m^2/d) followed by 11 months of subcutaneous maintenance treatment (10 MU/ m^2/d) administered 3 days a week. At 6.9 years' follow-up, the prolonged disease-free survival rate and overall survival rate in the INF-α2b arm of E1684 prompted US FDA approval of adjuvant high-dose INF-α2b.

The follow-up trial E1690 failed to confirm the efficacy of high-dose INF-α2b[176]; however, the study designs have been criticized for the following reasons[116]: (1) Unlike E1684, enrollment did not require pathologic staging with ELND or SLNB. (2) Patients were not stratified on the important prognostic feature of ulceration. (3) A disproportionate number of individuals from the observation arm crossed over into the INF-α2b arm in order to receive salvage therapy for recurrent disease. Any therapeutic benefit provided to this subgroup by INF-α2b went unrecognized given the intention to treat statistical analysis.

The most recent and largest of the three studies, ECOG 1694,[177] compared high-dose INF-α2b to an experimental vaccine (GM2-KLH21). This trail confirmed the efficacy of high-dose INF-α2b. The relapse-free and overall survival benefit observed in the high-dose INF-α2b control arm compared to the experimental vaccine arm was so compelling that the Data Safety Monitoring Committee terminated the trial early. More recently, the E1694 vaccine cohort has been found to have worse than expected survival rates compared to the interferon group, prompting concern about this form of therapy.[81]

Pooled analysis of E1684, E1690, and E1694 identified an improved relapse-free survival for high-risk melanoma patients undergoing adjuvant high-dose INF-α2b (p = 0.006).[178] An improvement in overall survival was not reported. A recent Cochrane review involving 18 randomized controlled trials with a total of 10,499 patients reported an improved DFS (HR = 0.83; p

< 0.00001) and overall survival (HR = 0.91; p = 0.003) for high-risk stage II and III patients receiving adjuvant INF-α2b.[179]

Although clinical trials continue to investigate alternative dosages and schedules,[180,181] only high-dose INF-α2b is FDA approved and used as routine adjuvant therapy within the United States. INF-α2b has significant toxicities to include flu-like symptoms, chronic fatigue (20% to 30%), neurologic side effects, depression and suicidal ideation, myelosuppression, thyroid dysfunction, and elevated liver enzymes.[176,177,182] Therefore, a thoughtful discussion with eligible at-risk patients about the risk/benefit ratio of adjuvant interferon treatment and their individual priorities with respect to quantity and quality of life is recommended.

Recent studies have focused on PEGylated interferon INF-α2b. The polyethylene glycol (PEG) covalently bonds to interferon, changing the pharmacokinetics to increase the drugs half-life. This change reduces the above toxicities and allows for a more convenient subcutaneous dosing schedule. EORTC 18991 was a phase III trial comparing PEGylated interferon to observation[183] for patients with completely resected stage III melanoma. At 7.6 years' follow-up, an improved recurrence-free but not overall survival rate was reported. Patients with microscopic nodal disease and ulcerated primary melanomas demonstrated greater benefit. In 2011, the FDA approved PEGylated interferon as adjuvant treatment for patients with stage III regional melanoma.

Targeted Agents

Given the significant toxicities associated with the above systemic therapies, research efforts have focused on targeted therapy. 2011 marked a landmark year for melanoma, with targeted agents receiving FDA approval for the treatment of advanced disease for the first time in over a decade.

In March 2011, the FDA approved *ipilimumab* for the treatment of stage IV melanoma. This monoclonal antibody targets cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), which ultimately sustains T-cell activation.[184,185] It is administered intravenously (3 mg/kg) once a week for four doses. A randomized control trial of patients with stage IV metastatic melanoma randomized to ipilimumab versus ipilimumab plus gp100 peptide vaccine and gp100 peptide vaccine alone demonstrated an overall survival

benefit with combined therapy (10 months; $p < 0.001$) and ipilimumab alone (10.1 months; $p = 0.003$) compared to vaccine only (6.4 months).[186] This improved overall survival rate was confirmed in a phase III randomized trial comparing ipilimumab and DTIC to DTIC alone.[187] Tumor response can take months. Only 20% of patients with melanoma respond to ipilimumab, but the response when present is long term. As many as 60% of patients experience immune-related side effects, the most common being diarrhea secondary to colitis. Patients with underlying autoimmune disorders are especially susceptible.

BRAF mutation has been identified in 42% of cutaneous melanomas include arthralgias (21%), development of cutaneous SCCs and keratoacanthomas (18%), and photosensitivity (12%). Approximately 38% of patients required dose modification to accommodate these side effects. A rapid response in days to weeks is common, but unfortunately, this response is not long term with a median response rate of 5 to 6 months. Since FDA approval of vemurafenib in August of 2011, two additional BRAF mutation–targeted agents have been approved. *Dabrafenib* is associated with fewer cutaneous SCCs and keratoacanthomas (6%).[81,188] Photosensitivity was also reduced compared to vemurafenib (6%), but pyrexia was more common (11%).

Trametinib is an inhibitor of MEK1/MEK2, a signaling molecule, which is downstream from BRAF in the MAP kinase signaling pathway. This orally administered adjuvant drug was studied in an open-label phase III clinical trial in patients with advanced metastatic melanoma.[189] The trametinib group demonstrated an improved progression-free survival (4.8 vs. 1.5 months; $p < 0.001$) and a 6-month survival (81% vs. 67%; $p = 0.01$). Unlike BRAF inhibitors, there were no incident of secondary skin lesions, but rash, diarrhea, and peripheral edema were commonly reported. The NCCN now recommends ipilimumab, vemurafenib, dabrafenib, and dabrafenib with trametinib as the preferred regimen for advanced or metastatic melanoma.[81]

KIT (c-kit) mutations are common to MMs and melanomas in sun-damaged sites.[38] *Imatinib* is a tyrosine kinase inhibitor known to inhibit KIT. Similar to the above BRAF inhibitors, molecular screening is imperative for appropriate patient selection. A phase II trial demonstrated a 23% overall response rate with imatinib.[190] Patients with KIT mutations involving exons

11 and 13 are most likely to respond; however, these responses have typically not been durable.[38]

FOLLOW-UP

The primary goals in the follow-up of patients who have been treated for melanoma are (1) early detection of locoregional recurrence, (2) early detection of a second melanoma (as well as nonmelanoma skin cancer), (3) psychosocial support for the patient and family, (4) patient education, and (5) detection of distant metastasis. Five to ten percent of melanoma patients go on to develop a second primary cancer during their lifetime.[73] This risk is lifelong and can occur anywhere on the skin. Thus, long-term, annual follow-up with a thorough total body examination is critical. Photodocumentation has proven helpful in following nevi.[191] Each office visit affords an opportunity to educate both patient and family members on the ABCDE warning signs, the importance of the use of sunscreen, the avoidance of sun during peak hours (11 AM to 2 PM), and the risks associated with tanning booths. The exact timing of follow-up appointments remains a debate. The current NCCN guidelines recommend skin surveillance at least once a year.[81] Regional ultrasound can be considered in patients who declined SLNB or who did not undergo TLND following a + SLN.[115] Ultimately, patient follow-up should be individualized and based on patient risk factors, family history, and level of anxiety.

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10 Cancer of the Nasal Cavity and the Paranasal Sinuses

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INTRODUCTION

Over the last two decades, significant advances have been made in both the diagnosis and management of cancer of the nasal cavity and paranasal sinuses. The most significant advances in diagnosis are office endoscopy and high-resolution imaging. These diagnostic tools have allowed more accurate delineation of the extent of sinonasal tumors and, hence, improved treatment planning. Significant advances in treatment include progress made in cranial base surgery allowing for safe excision of tumors involving the cranial base. In addition, the development of microvascular free tissue transfer has made effective reconstruction of more extensive surgical defects possible. Advances have also been made in both planning and delivery of radiotherapy such as intensity-modulated radiation therapy (IMRT) and proton therapy. Both modalities allow optimal radiation dosimetry to the tumor while sparing normal surrounding tissue. Various new combinations of effective cytotoxic chemotherapeutic and targeted biologic agents are also being increasingly incorporated in the overall management of patients with sinonasal cancer.

Recent advances made in diagnosis and treatment of patients with sinonasal cancer have clearly impacted our ability to control the disease and improve survival. Over the last 40 years, survival rates have improved from 25% to 40% in the 1960s to 65% to 75% in the last decade (**Fig. 10.1**). Despite these improvements, a significant number of patients die of their disease. The rarity of these tumors and the similarity of their presenting

symptoms to more common benign conditions, coupled with the propensity for early spread and involvement of surrounding critical structures, are reflected in the fact that most patients still present with advanced stage disease. This has clearly hampered attempts to further improve prognosis. In this chapter, we present the current trends in diagnosis, classification, staging, and treatment of patients with cancers of the nasal cavity and paranasal sinuses. We also discuss some of the strategies to improve the outcome of these patients.

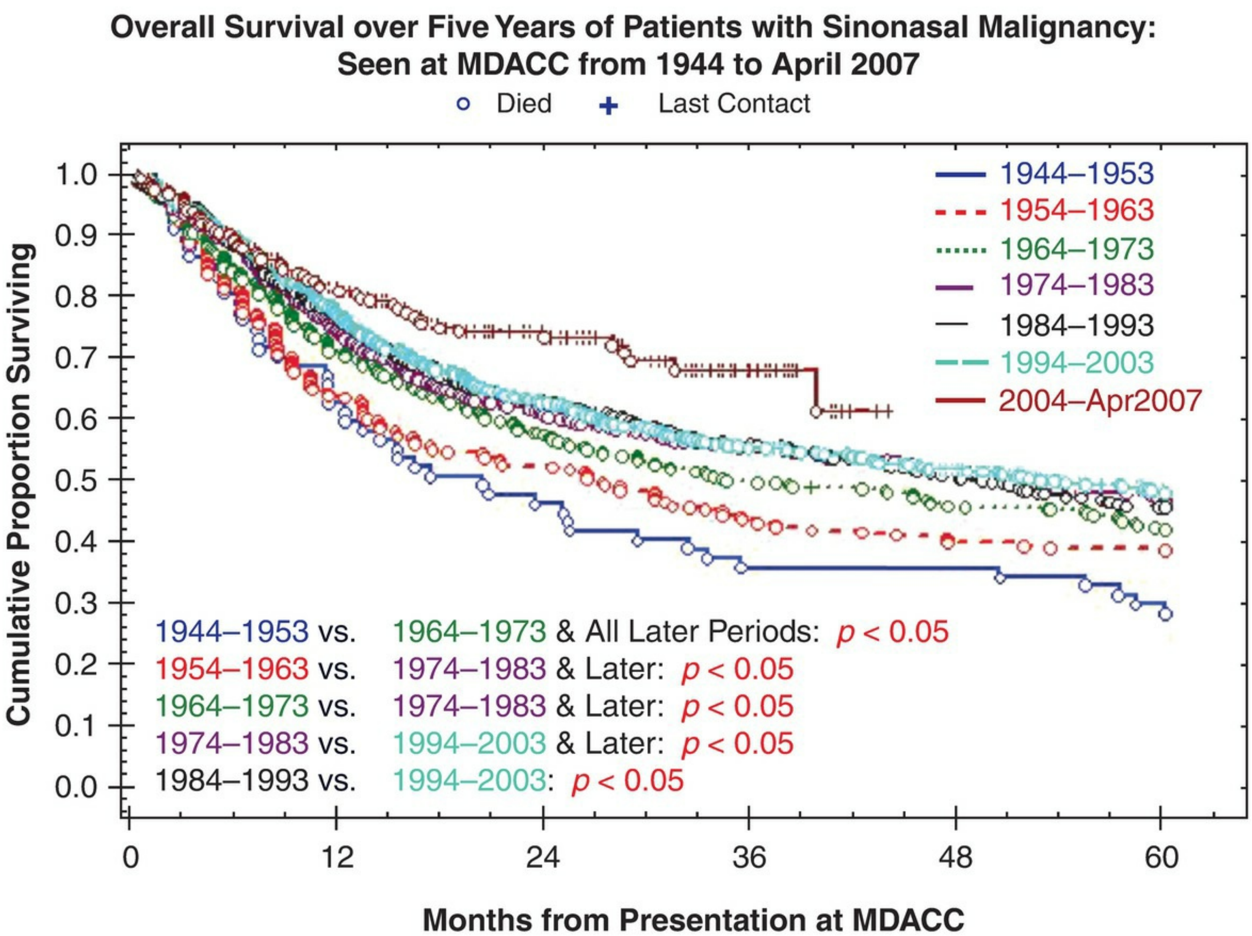


Figure 10.1. Improvement in 5-year OS of Patients with Sinonasal Malignancy. Data of 2,698 patients with sinonasal cancer seen at MD Anderson Cancer Center (MDACC) from 1944 to 2007.

ANATOMY

Nasal Cavity

The nasal cavity is bounded by the bony pyriform aperture and the external framework of the nose (**Fig.** 10.2**A**). The nasal cavity opens anteriorly through the skin-lined nasal vestibule into the nares and communicates posteriorly through the choanae with the nasopharynx (**Fig. 10.2B**). The nasal cavity is divided in the midline by the *nasal septum*, which includes both cartilaginous and bony components (**Fig. 10.2C**). The cartilage of the septum is somewhat quadrilateral in form and is thicker at its margins than at its center. Its anterior margin is connected with the nasal bones and is continuous with the anterior margins of the lateral cartilages; below, it is connected to the medial crura of the greater alar cartilages by fibrous tissue (Fig. 10.2A). Its posterior margin is connected with the perpendicular plate of the ethmoid, its inferior margin with the vomer and the palatine process of the maxilla.

On the *lateral nasal wall* are the superior, middle, and inferior nasal turbinates, and below and lateral to each turbinate (concha) is the corresponding nasal passage or meatus (**Fig.** 10.3**A and B**). Above the superior turbinate is a narrow recess, the sphenoethmoidal recess, into which the sphenoid sinus opens. The superior meatus is a short oblique passage extending about halfway along the upper border of the middle turbinate; the posterior ethmoid cells open into the front part of this meatus. The middle meatus is below and lateral to the middle turbinate. The anatomy of the middle meatus is fully displayed by removing the middle turbinate (Fig. 10.3A and B). The bulla ethmoidalis is the most prominent anterior ethmoid air cell. The hiatus semilunaris is a curved cleft lying below and in front of the bulla ethmoidalis. It is bounded inferiorly by the sharp concave margin of the uncinate process of the ethmoid bone and leads into a curved channel, the infundibulum, bounded above by the bulla ethmoidalis and below by the lateral surface of the uncinate process of the ethmoid. The anterior ethmoid air cells open into the front part of the infundibulum. The frontal sinus drains through the nasofrontal duct, which in ~50% of subjects will also drain into the infundibulum; but when the anterior end of the uncinate process fuses with the front part of the bulla, this continuity is interrupted and the frontonasal duct then opens directly into the anterior end of the middle meatus. Below the bulla ethmoidalis, and partly hidden by the inferior end of the uncinate process, is the ostium of the maxillary sinus. An accessory ostium from the maxillary sinus is frequently present below the posterior end of the middle nasal concha. The inferior meatus is below and lateral to the

inferior nasal turbinate. The nasolacrimal duct opens into the inferior meatus under cover of the anterior part of the inferior turbinate.

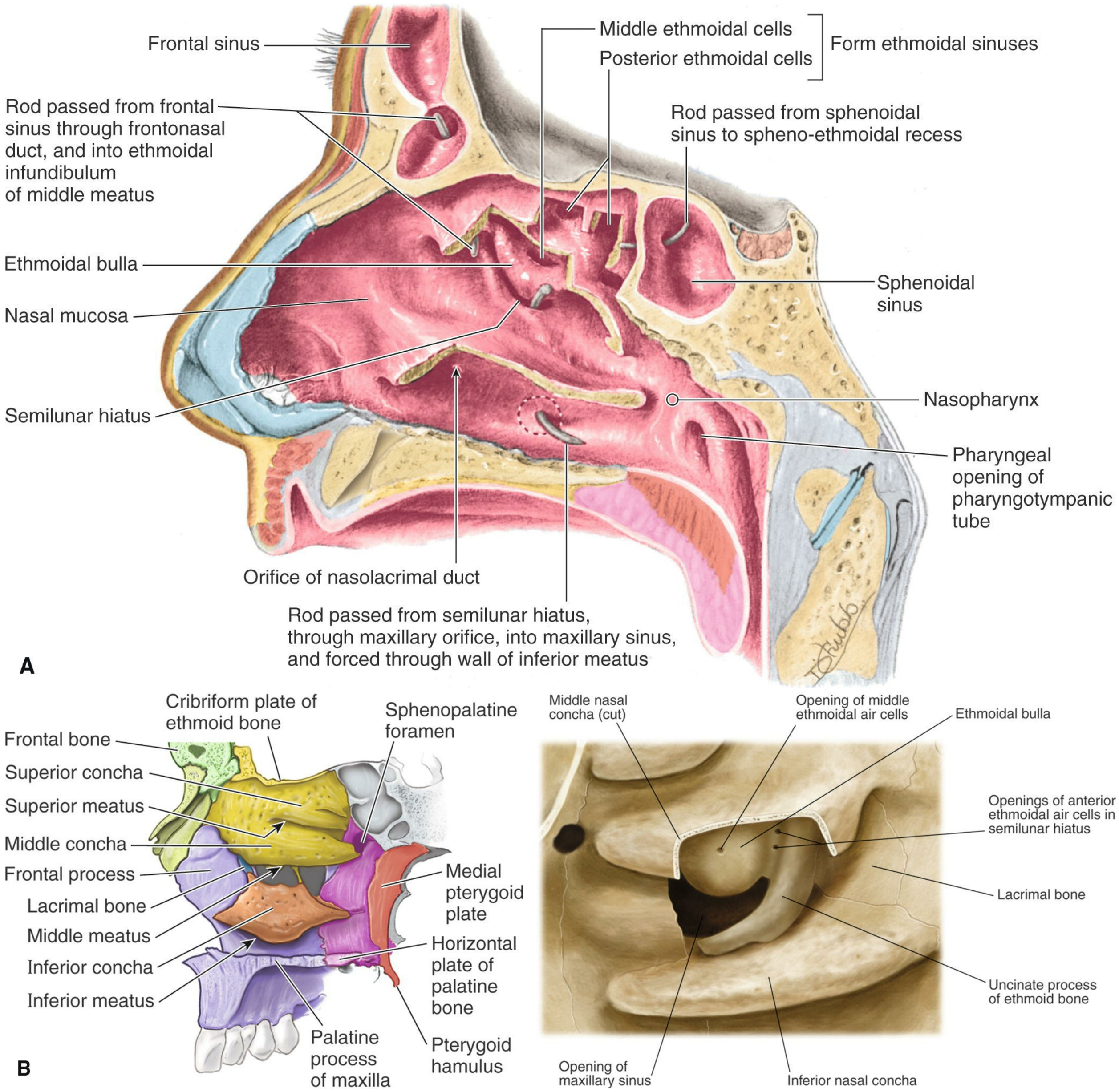


Figure 10.3. A: Anatomy of the lateral nasal wall. Removal of the middle turbinate demonstrates the anatomy of the middle meatus. (From Moore KL, Agur AMR, Dalley AF, eds. *Clinically Oriented Anatomy*. 7th ed. Philadelphia, PA: Wolters Kluwer Health; 2013.) **B:** Skeletal framework of the lateral nasal wall. Removal of the middle turbinate demonstrates the anatomy of the middle meatus. (Left image from Moore KL, Agur AMR, Dalley AF, eds. *Clinically Oriented Anatomy*. 7th ed. Philadelphia, PA:

Wolters Kluwer Health; 2013. Right image from Pansky B, Gest TR, eds. *Lippincott's Concise Illustrated Anatomy: Head and Neck* (vol. 3). Philadelphia, PA: Wolters Kluwer Health; 2014.)

The *roof* of the nasal cavity is narrow from side to side and slopes downward (at about a 30-degree angle) from front to back. The cribriform plate, which transmits the filaments of the olfactory nerve, forms the roof of the nasal cavity medial to the superior attachment of the middle turbinate. Lateral to the middle turbinate, the fovea ethmoidalis forms the roof of the ethmoid sinuses. Careful assessment of the anatomy of the nasal roof, especially the relationship of the cribriform plate to the fovea ethmoidalis, is critical in avoiding a cerebrospinal fluid (CSF) leak during surgery in this region. The cribriform plate is usually at a slightly lower horizontal plane than the fovea ethmoidalis forming a shallow olfactory groove. This configuration is known as Keros type I (**Fig. 10.4**). However, the cribriform plate may be moderately or significantly lower than the fovea ethmoidalis resulting in a medium (Keros type II) or deep (Keros type III) olfactory groove. The topography of the roof may also be asymmetrical (Fig. 10.4).

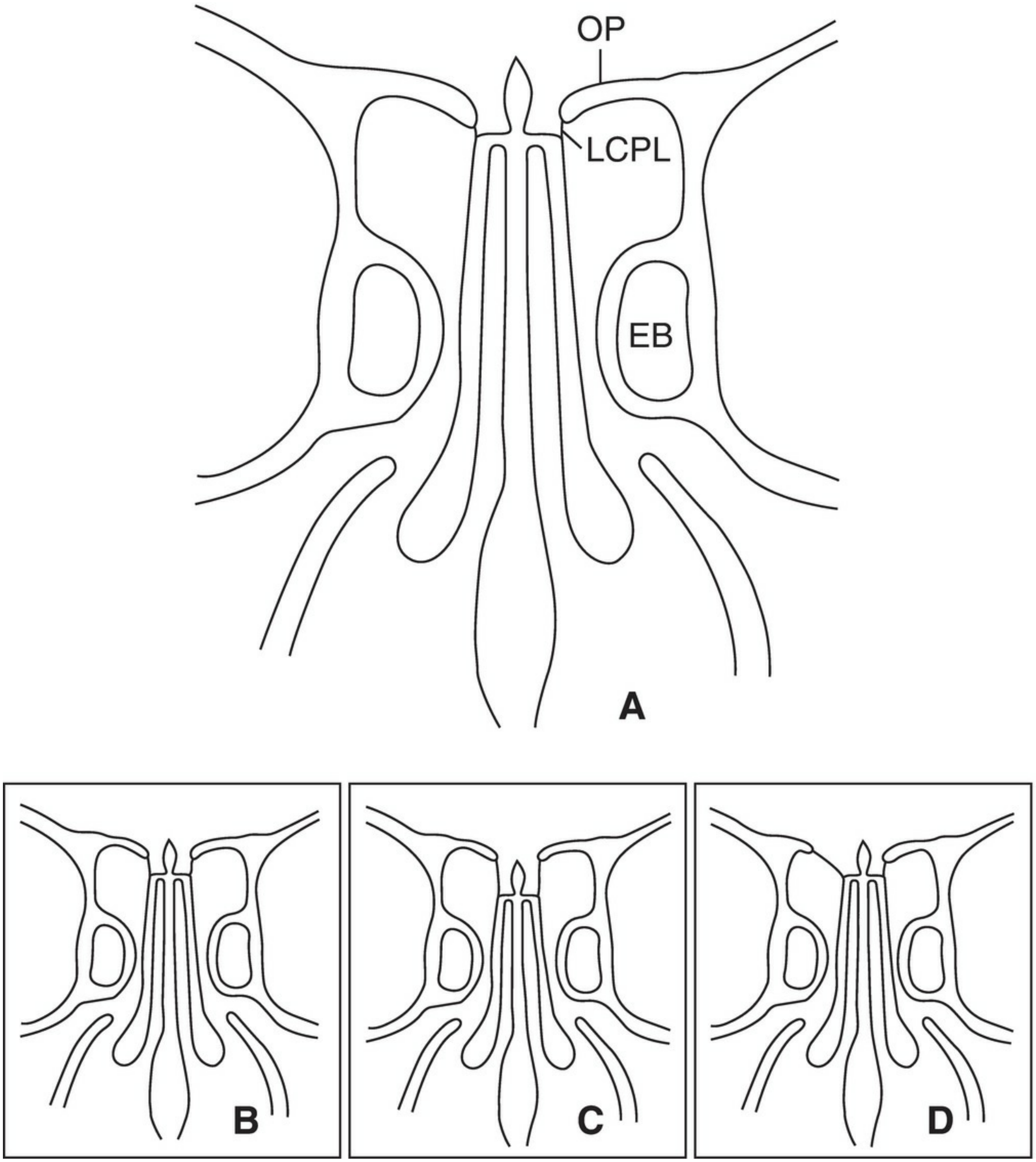


Figure 10.4. Anatomy of the ethmoid roof and lateral lamella of the cribriform plate. **A:** Keros type I. **B:** Keros type II. **C:** Keros type III. **D:** Asymmetrical ethmoid roof. Note that the right lateral lamella of the cribriform plate is very thin and long and is obliquely oriented including much of the right ethmoid roof. OP, orbital plate of frontal bone; LCPL, lateral cribriform plate lamella; EB, ethmoid bulla.

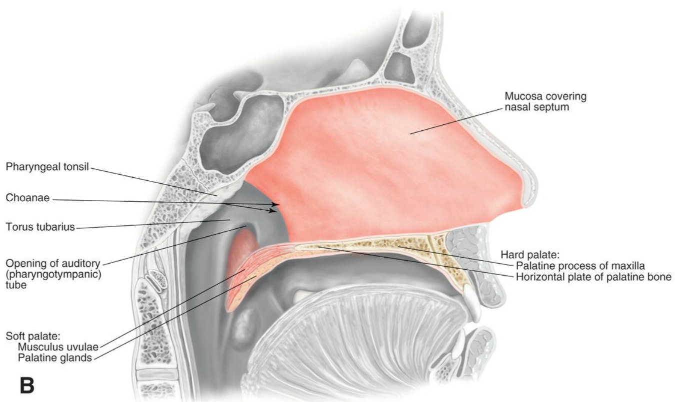
The *floor* of the nasal cavity is concave from side to side and almost horizontal anteroposteriorly. The palatine process of the maxilla forms the anterior three-fourths, and the horizontal process of the palatine bone forms the posterior fourth of the nasal floor (Fig. 10.2C).

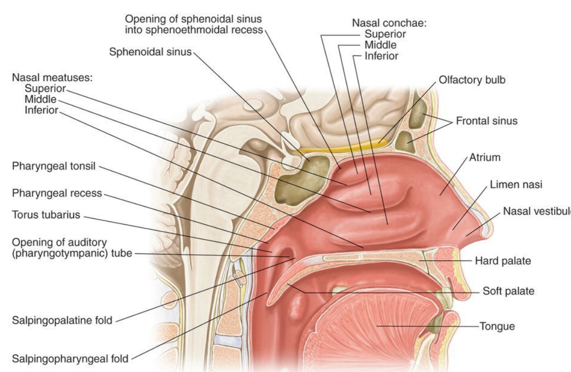
The majority of the nasal cavity is lined by pseudostratified ciliated columnar epithelium, which contains mucous and serous glands (respiratory epithelium). Specialized olfactory epithelium lines the most superior portion of the nasal cavity and has direct connections with the olfactory tracts through openings in the cribriform plate.

The *arteries* of the nasal cavities are the anterior and posterior ethmoidal branches of the ophthalmic artery, which supply the ethmoid and frontal sinuses and roof of the nose. The sphenopalatine artery supplies the mucous membrane covering the lateral nasal wall. The septal branch of the superior labial artery supplies the anterior inferior septum. The *veins* form a close cavernous plexus beneath the mucous membrane. This plexus is especially well marked over the lower part of the septum and over the middle and inferior turbinates. Venous drainage follows a pattern similar to arterial supply. The *lymphatic drainage* from the anterior part of the nasal cavity, similar to that of the external nose, is to the submandibular group of lymph nodes (level I). Lymphatics from the posterior two-thirds of the nasal cavities and from the paranasal sinuses drain to the upper jugular (level II) and retropharyngeal lymph nodes.

The sensory *nerves* of the nasal cavity transmit either somatoautonomic or olfactory sensation. *Somatoautonomic* nerves include the nasociliary branch of the ophthalmic, which supplies the anterior septum and lateral wall. The anterior alveolar nerve, branch of the maxillary (V2), supplies the inferior meatus and inferior turbinate. The nasopalatine nerve supplies the middle of the septum. The anterior palatine nerve supplies the lower nasal branches to the middle and inferior turbinates. The nerve of the pterygoid canal (vidian) and the nasal branches from the sphenopalatine ganglion supply the upper and posterior septum and superior turbinate. The *olfactory nerve* fibers arise from the bipolar olfactory cells and unite in fasciculi, which form a plexus beneath the mucous membrane and then ascend passing into the skull through the foramina in the cribriform plate. Intracranially, olfactory nerve fibers enter the under surface of the olfactory bulb, in which they ramify and form synapses with the dendrites of the mitral cells of the

olfactory tract.





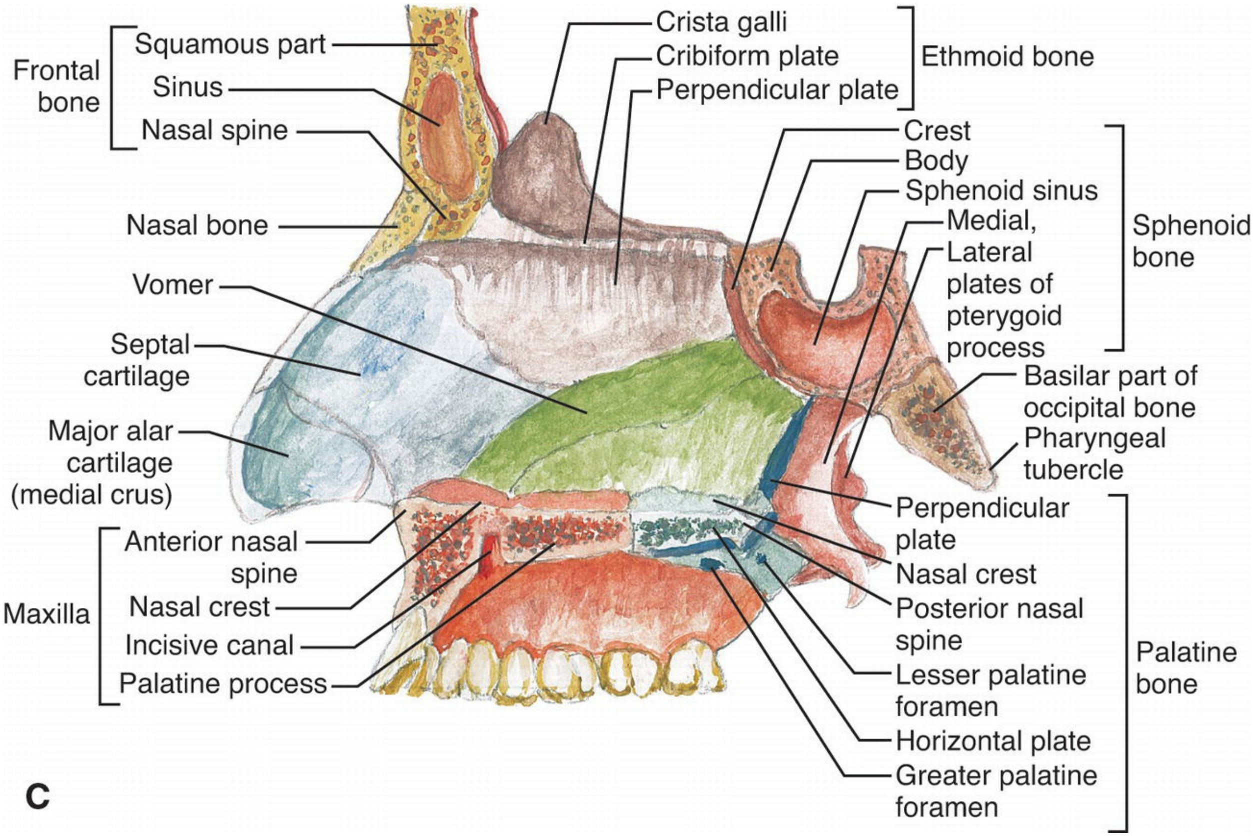


Figure 10.2. A: Anatomy of the external nose. (From Chung KW, Chung HM, Halliday NL, eds. *Gross Anatomy*. 8th ed. Philadelphia, PA: Wolters Kluwer; 2015.) B:Anatomy of the nasal septum. (From Pansky B, Gest TR, eds. *Lippincott's Concise Illustrated Anatomy: Head and Neck* (vol. 3). Philadelphia, PA: Wolters Kluwer Health; 2014.) C:Skeletal framework of the nasal septum. (From Chung KW, Chung HM, Halliday NL, eds. *Gross Anatomy*. 8th ed. Philadelphia, PA: Wolters Kluwer; 2015.)

Maxillary Sinus

The maxillary sinus (*antrum of Highmore*), the largest of the accessory sinuses of the nose, is a pyramidal cavity in the body of the maxilla (**Figs. 10.5 and 10.6**). Its base is formed by the lateral wall of the nasal cavity, and its apex extends into the zygomatic process. Its roof or orbital wall is frequently ridged by the infraorbital canal, whereas its floor is formed by the alveolar process of the maxilla and is usually 1 to 10 mm below the level of the floor of the nose. Projecting into the floor are several conical elevations corresponding with the roots of the first and second molar teeth, and in some cases, the floor is perforated by one or more of these roots. The natural

ostium of the maxillary sinus is partially covered by the uncinate process and communicates with the lower part of the hiatus semilunaris of the lateral nasal wall (Figs. 10.3 and 10.5). An accessory ostium is frequently seen in, or immediately behind, the hiatus. The maxillary sinus appears as a shallow groove on the medial surface of the bone about the 4th month of fetal life but does not reach its full size until after the second dentition.

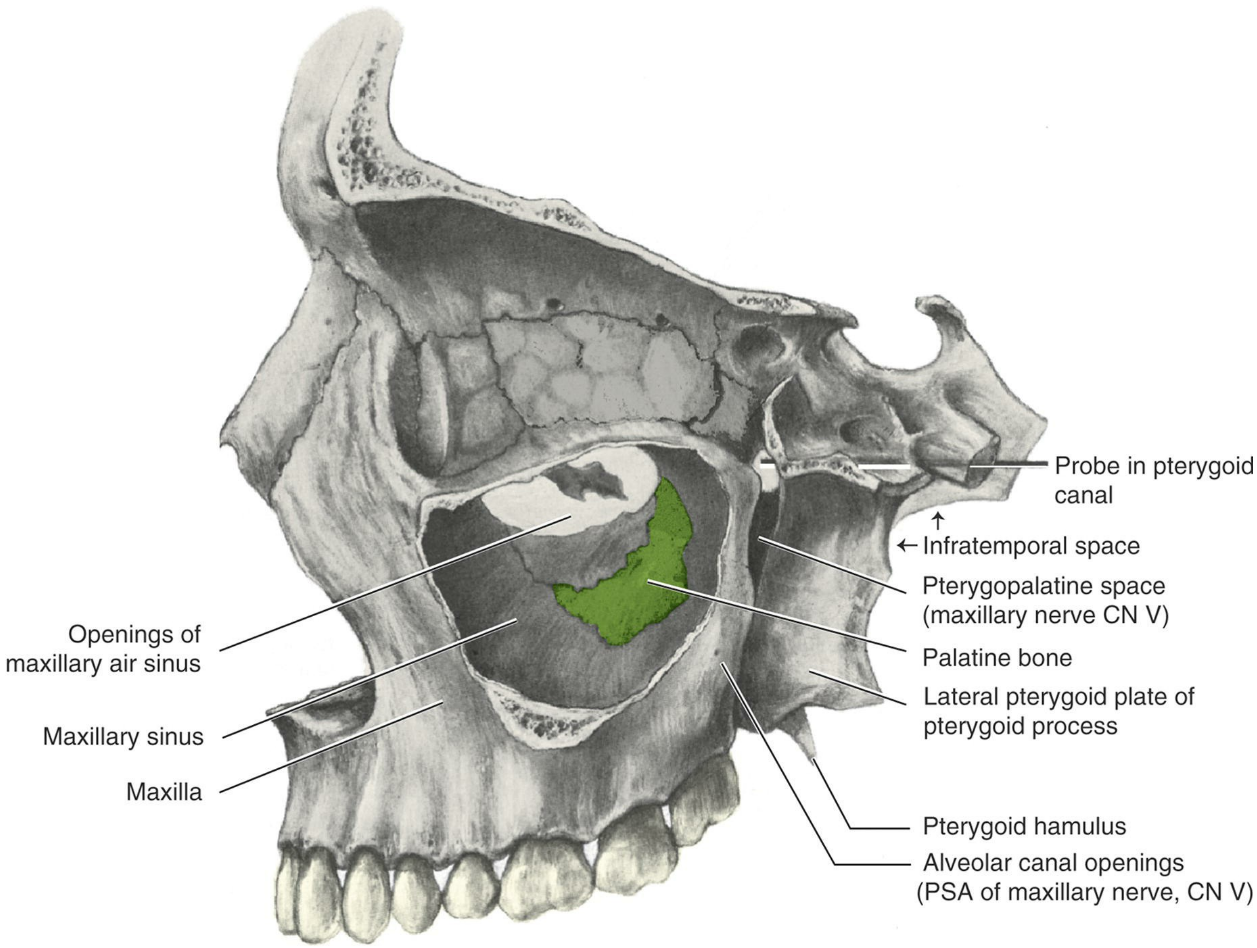


Figure 10.5. Anatomy of the maxillary sinus (lateral wall removed). (From Scheid RC, Weiss G, eds. *Woelfel's Dental Anatomy*. 8th ed. Philadelphia, PA: Wolters Kluwer Health; 2012.)

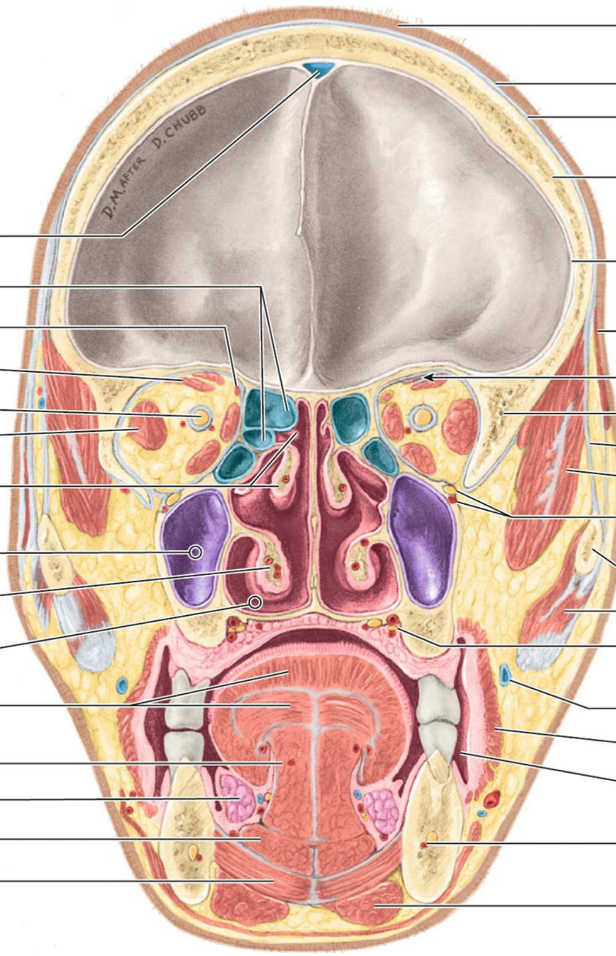


Figure 10.6. Anatomy of the ethmoid and maxillary sinuses (Coronal section). (From Moore KL, Agur AMR, Dalley AF, eds. *Clinically Oriented Anatomy*. 7th ed. Philadelphia, PA: Wolters Kluwer Health; 2013.)

Ethmoid Sinus

The ethmoidal air cells consist of numerous thin-walled cavities situated in the ethmoidal labyrinth and bounded by the frontal, maxillary, lacrimal, sphenoid, and palatine bones. They lie in the upper part of the nasal cavity between the orbits (Fig. 10.6). The ethmoid sinuses are separated from the orbital cavity by a thin bony plate, the lamina papyracea. On either side, they are arranged in three groups, *anterior*, *middle*, and *posterior*. The anterior and middle groups open into the middle meatus of the nose, the former by way of the infundibulum, and the latter on or above the bulla ethmoidalis (Fig. 10.3). The posterior cells open into the superior meatus under cover of the superior nasal concha. Sometimes one or more ethmoid air cells extend over the

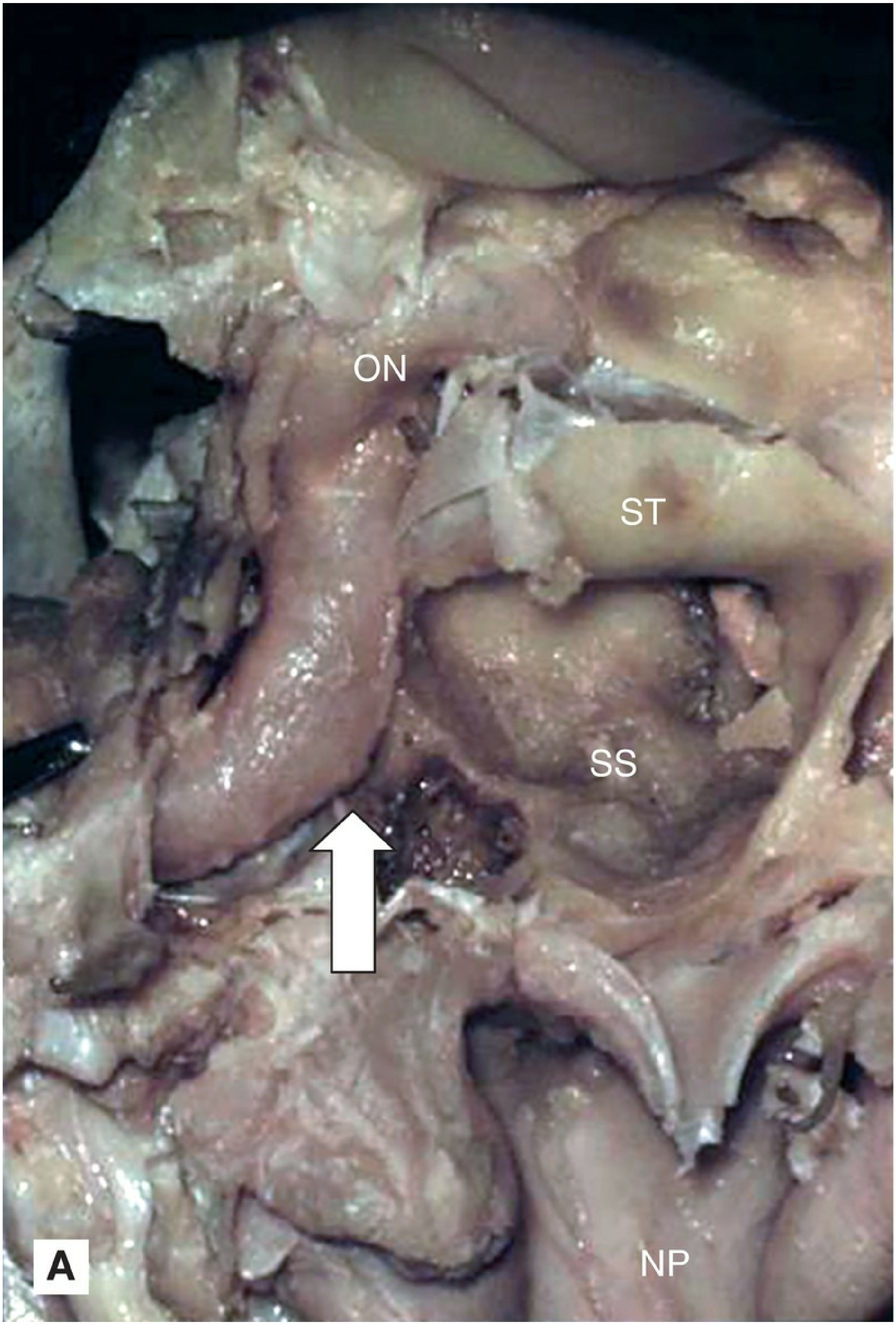
orbital cavity (supraorbital ethmoid cells) or the optic nerve (Onodi cell). The ethmoidal cells begin to develop during fetal life.

Frontal Sinus

The paired frontal sinuses appear to be outgrowths from the most anterior ethmoidal air cells. They are situated behind the superciliary arches, are rarely symmetrical, and the septum between them frequently deviates to one or the other side of the middle line. Absent at birth, the frontal sinuses are generally fairly well developed between the 7th and 8th years but only reach their full size after puberty. The frontal sinus is lined with respiratory epithelium and drains into the anterior part of the corresponding middle meatus of the nose through the frontonasal duct, which traverses the anterior part of the labyrinth of the ethmoid. The soft tissues of the forehead are located anteriorly, the orbits are located inferiorly, and the anterior cranial fossa is located posteriorly (Fig. 10.3). Blood and neural supply is from the supraorbital and supratrochlear neurovascular bundles.

Sphenoid Sinus

The sphenoid sinus begins at the most posterior and superior portion of the nasal cavity (Fig. 10.3). This midline structure, which is contained within the body of the sphenoid bone, is irregular and often has an eccentrically located intersinus septum. When exceptionally large, the sphenoid sinus may extend into the roots of the pterygoid processes or great wings and may pneumatize the basilar part of the occipital bone. The sphenoid sinus ostium is located on the anterior wall of the sinus and communicates directly with the sphenoethmoidal recess above and medial to the superior turbinate (Fig. 10.3). The sphenoid sinuses are present as minute cavities at birth, but their main development takes place after puberty. The posterior superior wall of the sphenoid sinus displays the forward convexity caused by the floor of the sella turcica, which contains the pituitary gland. The optic nerve and the internal carotid artery are closely related to the superior lateral wall of the sphenoid sinus, and their bony canals may be dehiscent within the sinus cavity (**Fig. 10.7**). Vascular and neural supplies come from the sphenopalatine and posterior ethmoidal arteries and the branches of the sphenopalatine ganglion, respectively.



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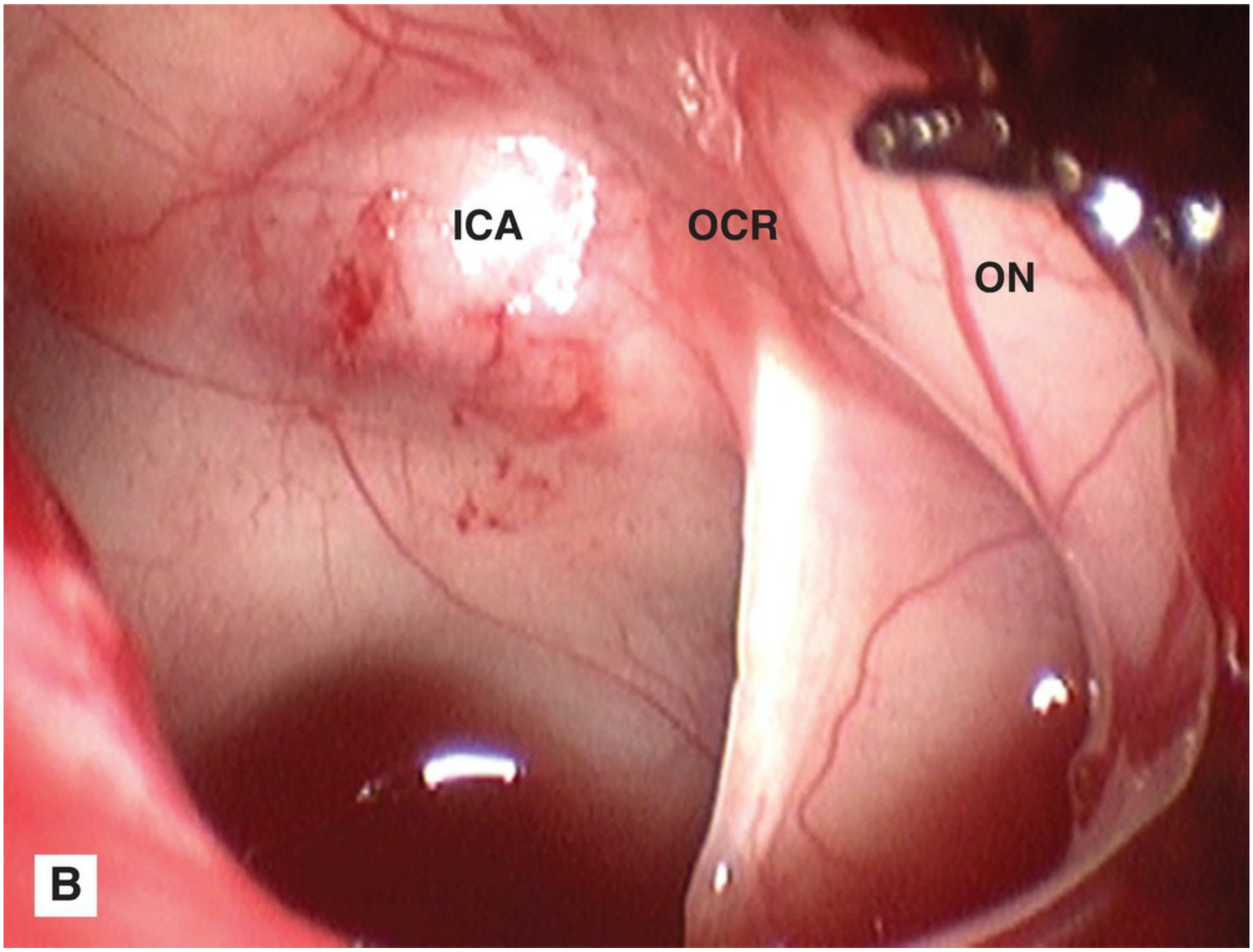
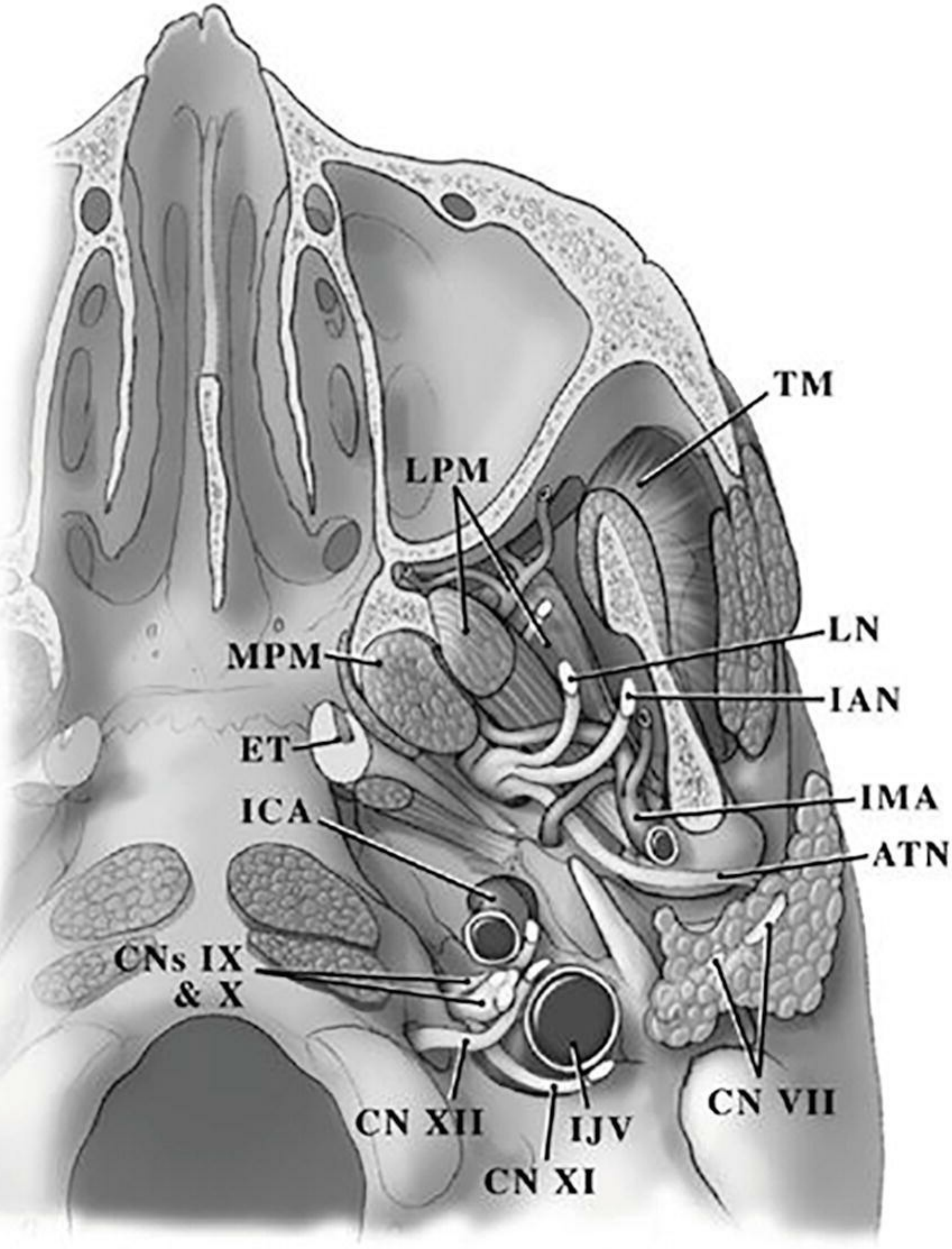


Figure 10.7. A: Cadaver dissection of the sphenoid sinus (SS). The sinus is located in the midline superior to the nasopharynx (NP). The sella turcica (ST) forms a convexity in the posterior superior wall. The internal carotid artery (*arrow*) courses through the lateral wall of the sinus and is related superiorly to the optic nerve (ON). **B:** Endoscopic view of the left sphenoid sinus. Note the internal carotid artery (ICA) and optic nerve (ON) impressions on the lateral and superior walls. A bony septum within the sinus inserts into the opticocarotid recess (OCR).

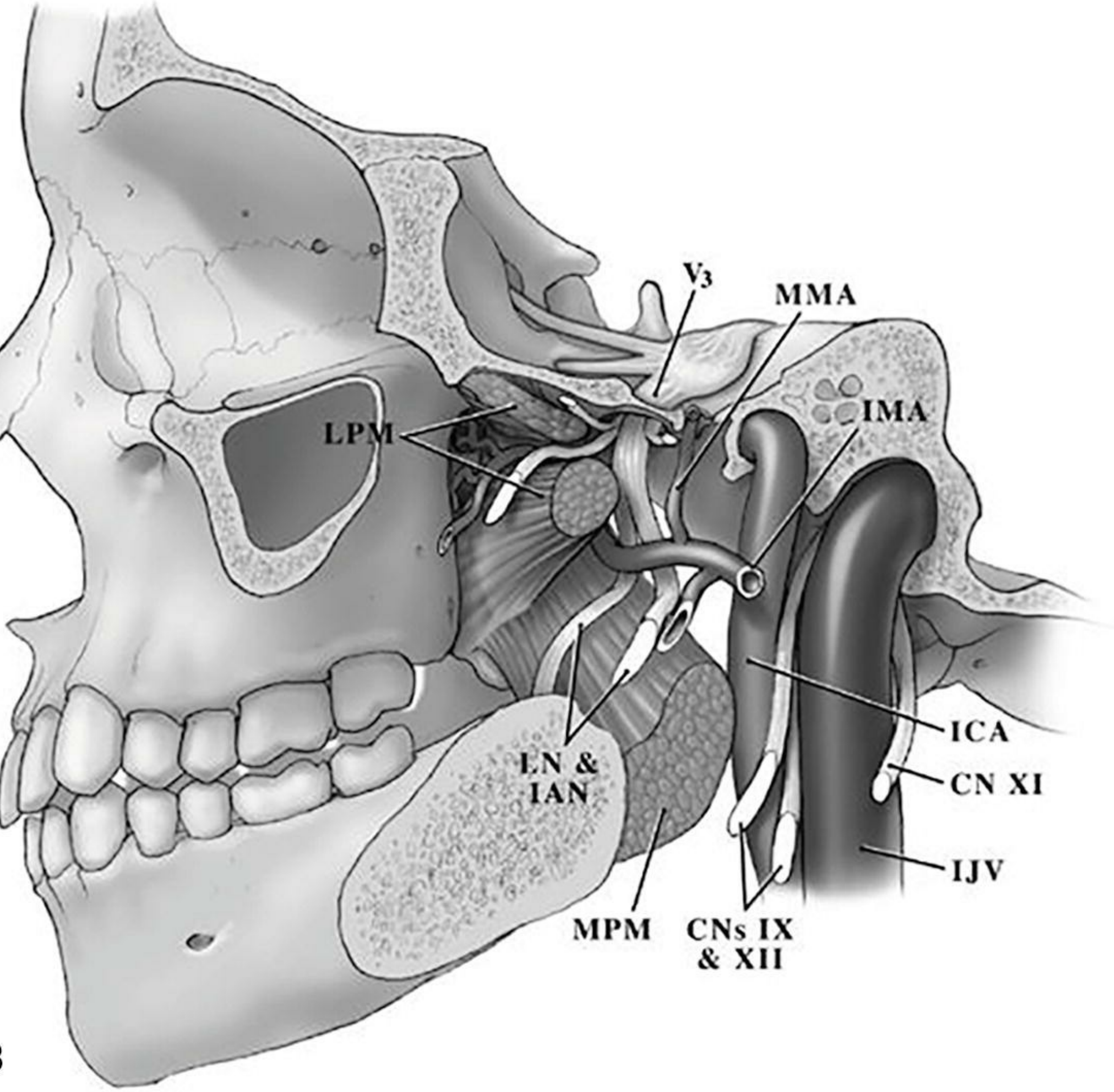
Infratemporal Fossa

The infratemporal fossa is an irregularly shaped space, situated below and medial to the zygomatic arch. It is bounded anteriorly by the posterior surface of the maxilla; superiorly by the greater wing of the sphenoid and by the under surface of the squamous portion of the temporal bone; medially by the lateral pterygoid plate; and laterally by the ramus of the mandible. It contains the inferior aspect of the temporalis muscle and the medial and lateral

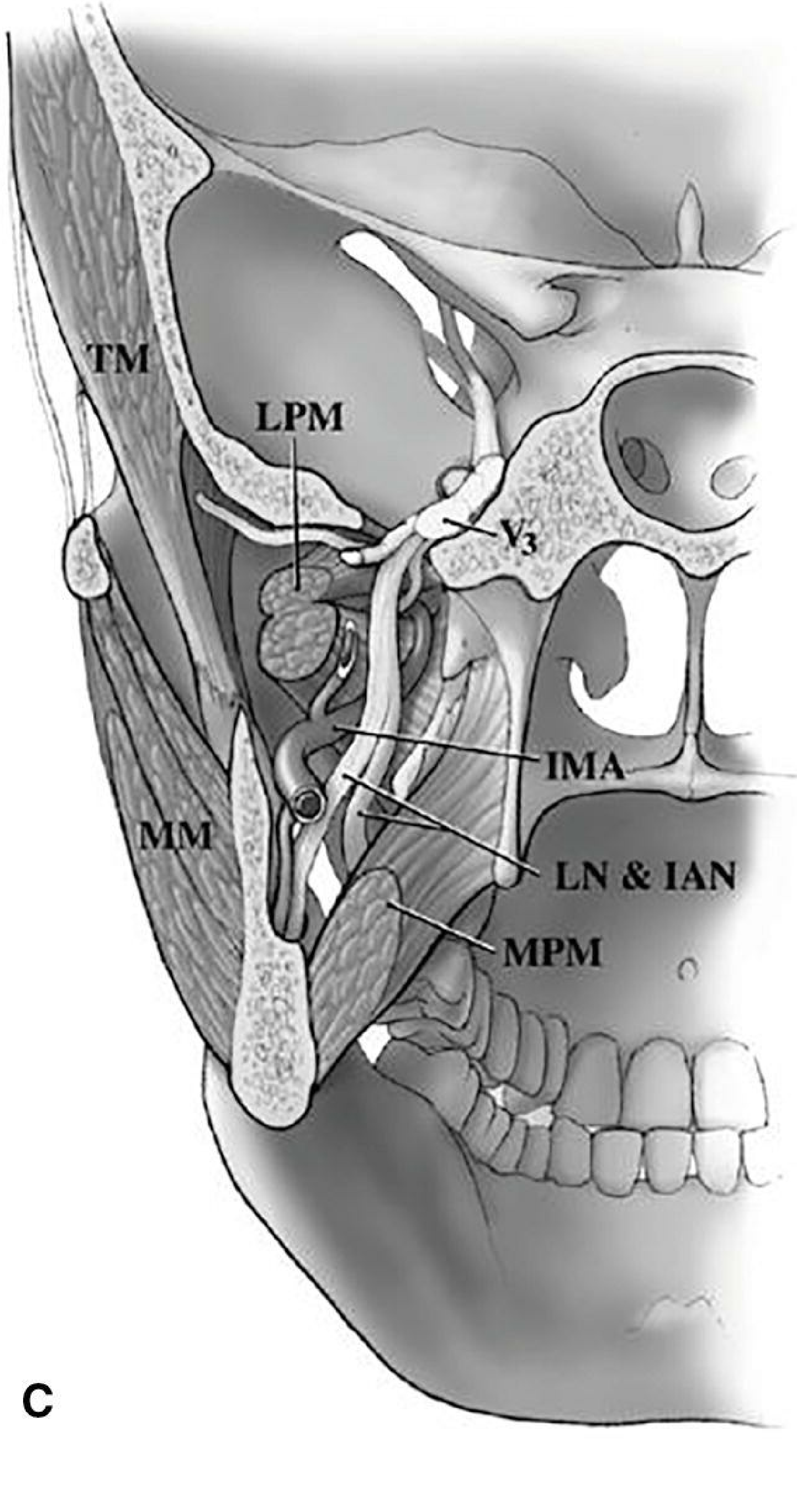
pterygoid muscles (Fig. 10.8). It also contains branches of the internal maxillary vessels including the middle meningeal artery and the mandibular (V3) nerves including the lingual, inferior alveolar, and auriculotemporal nerves. The foramen ovale and foramen spinosum open on its roof and the alveolar canals on its anterior wall. The inferior orbital and pterygomaxillary fissures communicate with and may act as routes of spread of cancer to the infratemporal fossa. The infratemporal fossa also contains the upper carotid sheath including the internal carotid artery, internal jugular vein, and the last four cranial nerves (Fig. 10.8).



A



B



C

Figure 10.8. Anatomy of the infratemporal fossa: (**A**) inferior view, (**B**) lateral view, and (**C**) anterior view. TM, temporalis muscle; MM, masseter muscle; MPM, medial pterygoid muscle; LPM, lateral pterygoid muscle; IMA, internal maxillary artery; MMA, middle meningeal artery; ICA, internal carotid artery; IJV, internal jugular vein; LN, lingual nerve; IAN, inferior alveolar nerve; ATN, auriculotemporal nerve; V3, third division of the trigeminal nerve; ET, eustachian tube; CN, cranial nerve (VII, IX, X, XI, and XII).

Pterygopalatine Fossa

The pterygopalatine fossa (PPF) is a small, triangular space situated behind the maxillary sinus, in front of the pterygoid plates, and beneath the apex of the orbit. This fossa communicates with the orbit by the inferior orbital fissure, with the nasal cavity by the sphenopalatine foramen, and with the infratemporal fossa by the pterygomaxillary fissure (Fig. 10.5). Five foramina open into it. Of these, three are on the posterior wall, which are the *foramen rotundum*, the *pterygoid canal*, and the *pharyngeal canal*, in this order downward and medial. On the medial wall is the *sphenopalatine foramen*, and below is the superior orifice of the *pterygopalatine canal* (Fig. 10.5). The fossa contains the maxillary nerve, the sphenopalatine ganglion, and the terminal part of the internal maxillary artery. The fissures and foramina of the PPF serve as “highways” for spread of cancer from the sinonasal region to the orbit, infratemporal fossa, and cranial base.

Anterior Cranial Fossa

The floor of the anterior fossa is formed by the orbital plates of the frontal bone, the cribriform plate of the ethmoid, and the lesser wings and front part of the body of the sphenoid. In the midline, it presents, from anterior to posterior, the *frontal crest* for the attachment of the falx cerebri; the *foramen cecum*, which usually transmits a small vein from the nasal cavity to the superior sagittal sinus (SSS); and the *crista galli*, the free margin of which affords attachment to the falx cerebri (**Fig. 10.9**). On either side of the crista galli is the *olfactory groove* formed by the cribriform plate, which supports the olfactory bulb and presents foramina for the transmission of the olfactory nerves. Lateral to either olfactory groove are the internal openings of the anterior and posterior ethmoidal foramina; the anterior, situated about the

middle of the lateral margin of the olfactory groove transmits the anterior ethmoidal vessels and the nasociliary nerve; the nerve runs in a groove along the lateral edge of the cribriform plate; and the posterior ethmoidal foramen opens at the back part of this margin under cover of the projecting lamina of the sphenoid and transmits the posterior ethmoidal vessels and nerve. More laterally, the cranial floor forms the orbital roof and supports the frontal lobes of the cerebrum. Farther back in the middle is the planum sphenoidale, forming the roof of the sphenoid sinus, and the anterior margin of the chiasmatic groove, running laterally on either side to the upper margin of the optic foramen (Fig. 10.9).

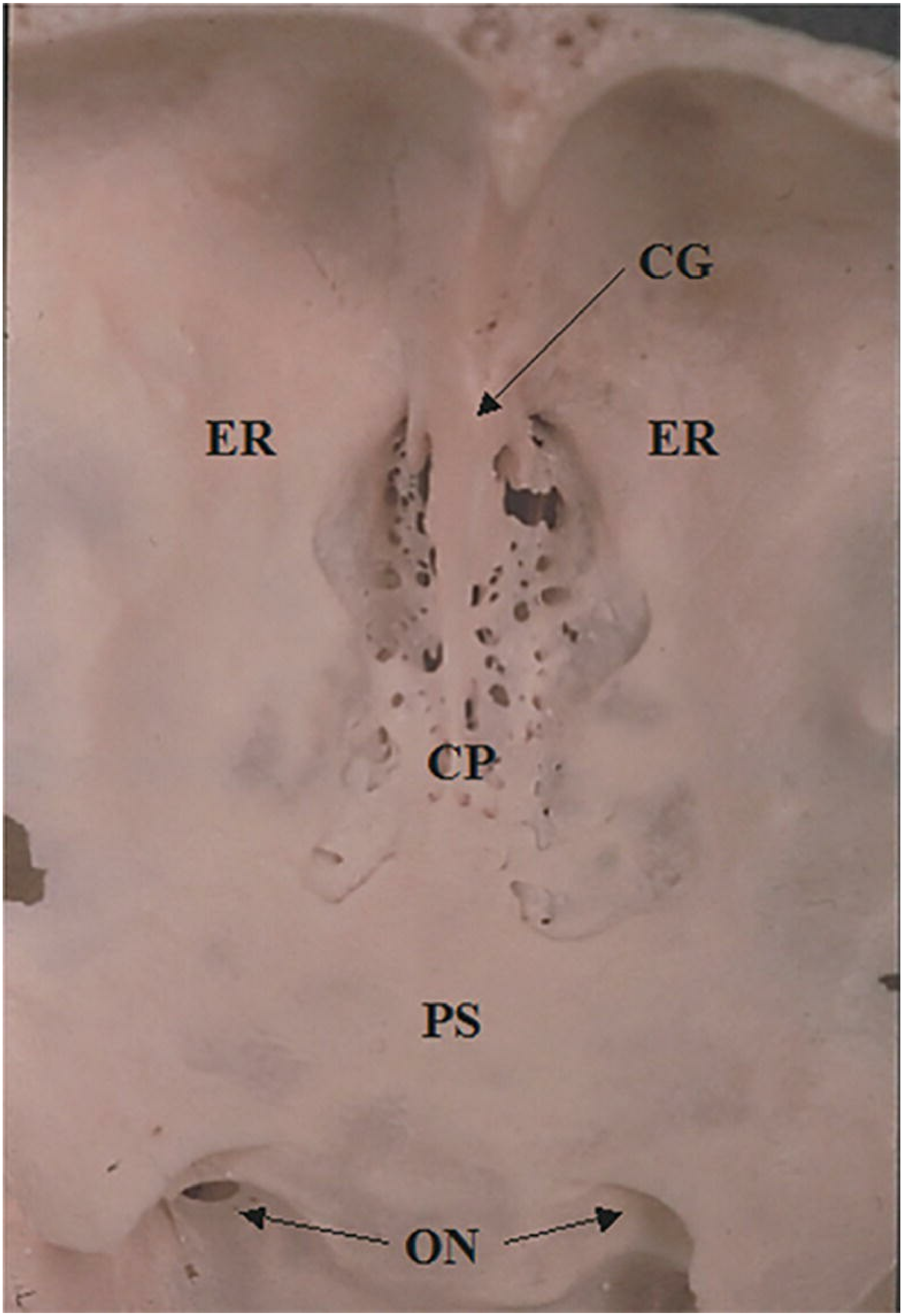

CG
ER
ER
CP
PS
ON

Figure 10.9. The floor of the anterior cranial fossa. The cribriform plate (CP) is characterized by the presence of foramina for the olfactory nerves on each side of the crista galli (CG), which is seen in the midline. Lateral to the CP is the ethmoidal roof (ER) and even more lateral the roof of the orbit. Posterior to the cribriform plate is the planum sphenoidale (PS). The optic nerves (ON) form the optic chiasm behind the planum sphenoidale.

Orbit

The orbits are two quadrilateral pyramidal cavities, their bases being directed forward and lateral, and their apices backward and medial, so that their long axes diverge at a 45-degree angle and if continued backward would meet over the body of the sphenoid. The orbit is anatomically defined by seven bones (**Fig. 10.10**): frontal, zygomatic, maxillary, lacrimal, ethmoid, sphenoid, and palatine, and by the orbital septum, which originates at the arcus marginalis, fusing with the levator aponeurosis above and the capsulopalpebral fascia below. It is bounded by the ethmoid and sphenoid sinuses at its medial aspect, the frontal sinus superomedially, the cranial vault superiorly and posteriorly, the temporal fossa laterally, and the maxillary sinus inferiorly. Each orbital cavity has a *roof*, a *floor*, a *medial* and a *lateral wall*, a *base*, and an *apex.*

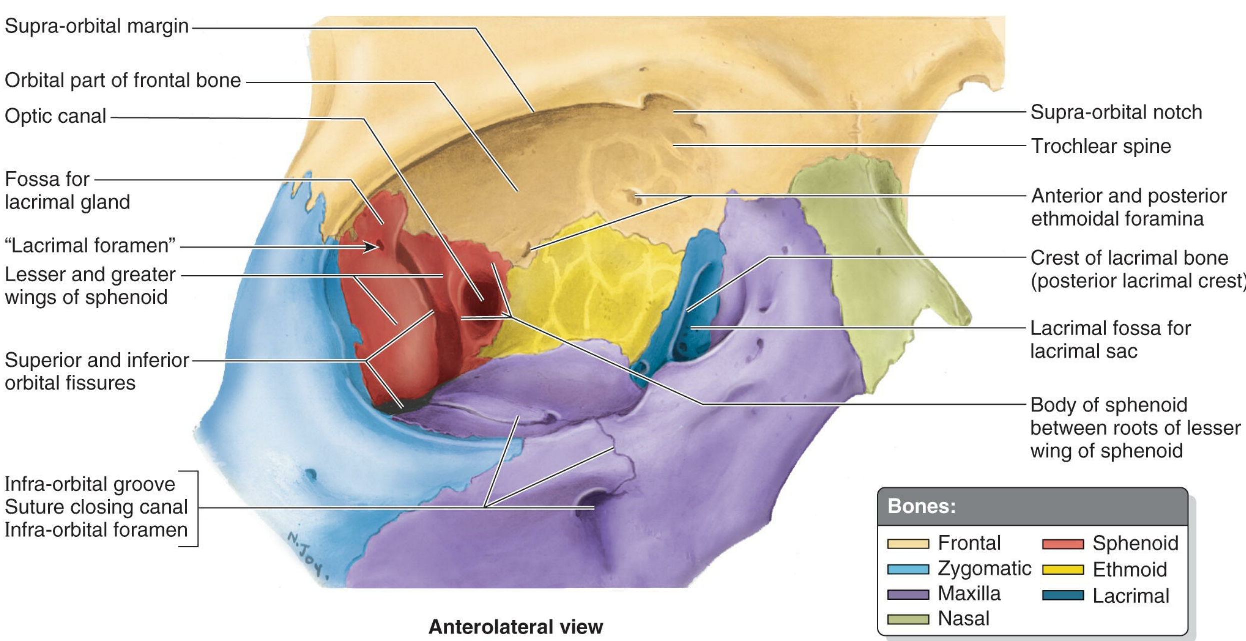


Figure 10.10. Anatomy of the right orbit. (From Moore KL, Agur AMR,

Dalley AF, eds. *Clinically Oriented Anatomy*. 7th ed. Philadelphia, PA: Wolters Kluwer Health; 2013.)

The *roof* is formed anteriorly by the orbital plate of the frontal bone and posteriorly by the lesser wing of the sphenoid. It presents *medially* the *trochlear fovea* for the attachment of the cartilaginous pulley of the superior oblique muscle and *laterally* the *lacrimal fossa* for the lacrimal gland.

The *floor* is formed mainly by the orbital surface of the maxilla, anteriorly and *laterally* by the orbital process of the zygomatic bone, and posterior and *medially*, to a small extent, by the orbital process of the palatine bone. At its medial angle is the superior opening of the nasolacrimal canal, immediately to the lateral side of which is a depression for the origin of the inferior oblique muscle. Running anteriorly near the middle of the floor is the *infraorbital canal*, ending anterior to the maxilla in the infraorbital foramen and transmitting the infraorbital nerve and vessels.

The *medial wall* is formed anteriorly to posteriorly by the frontal process of the maxilla, the lacrimal bone, the lamina papyracea of the ethmoid, and a small part of the body of the sphenoid anterior to the optic foramen. Anteroinferiorly, the lacrimal sac is situated between the anterior and posterior lacrimal crests at the junction between the medial wall and the floor. The lacrimal part of the orbicularis oculi arises from the posterior lacrimal crest. At the junction of the medial wall and the roof, the frontoethmoidal suture presents the *anterior* and *posterior ethmoidal foramina*, the former transmitting the nasociliary nerve and anterior ethmoidal vessels and the latter the posterior ethmoidal nerve and vessels. These foramina indicate the level of the cranial base within the orbit.

The *lateral wall* is formed by the orbital process of the zygomatic and the orbital surface of the greater wing of the sphenoid. On the orbital process of the zygomatic bone are the orbital tubercle (Whitnall) and the orifices of one or two canals, which transmit the branches of the zygomatic nerve. Between the roof and the lateral wall, near the apex of the orbit, is the *superior orbital fissure (SOF)*. Through this fissure, the oculomotor, the trochlear, the ophthalmic division of the trigeminal (V1), and the abducens nerves enter the orbital cavity, also some filaments from the cavernous plexus of the sympathetic and the orbital branches of the middle meningeal artery. Passing posteriorly through the fissure are the ophthalmic vein and the recurrent

branch from the lacrimal artery to the dura mater. The lateral wall and the floor are separated posteriorly by the *inferior orbital fissure*, which transmits the maxillary nerve (V2) and its zygomatic branch, the infraorbital vessels, and the ascending branches from the sphenopalatine ganglion.

The *base* of the orbit (orbital rim), quadrilateral in shape, is formed superiorly by the supraorbital arch of the frontal bone, in which is the *supraorbital notch* or *foramen* for the passage of the supraorbital vessels and nerve; inferiorly by the zygomatic bone and maxilla, united by the zygomaticomaxillary suture; *laterally* by the zygomatic bone and the zygomatic process of the frontal joined by the zygomaticofrontal suture; and *medially* by the frontal bone and the frontal process of the maxilla united by the frontomaxillary suture.

The *apex* is situated in the posterior aspect of the orbit. The optic foramen is a short, cylindrical canal, through which passes the optic nerve and ophthalmic artery.

The *extraocular muscles*—four rectus muscles and two obliques—effect movement of the eye. The third cranial nerve innervates all but the lateral rectus and the superior oblique muscles, which are innervated by the fourth and sixth cranial nerves, respectively. The rectus muscles originate at the annulus of Zinn and insert on the globe forming a muscle cone, which is the central anatomic space in the orbit.

The *lacrimal system* is composed of secretory and drainage systems. Secretory glands—the glands of Moll, Krause, and Wolfring—may be found along the margin of the eyelid. The lacrimal gland with its palpebral and orbital lobes is located in the superotemporal orbit (**Fig. 10.11**). The lacrimal drainage system, located in the inferonasal orbit, is represented by the puncta, canaliculi, lacrimal sac, and nasolacrimal duct. Tumor involvement of the lacrimal system may present with epiphora.

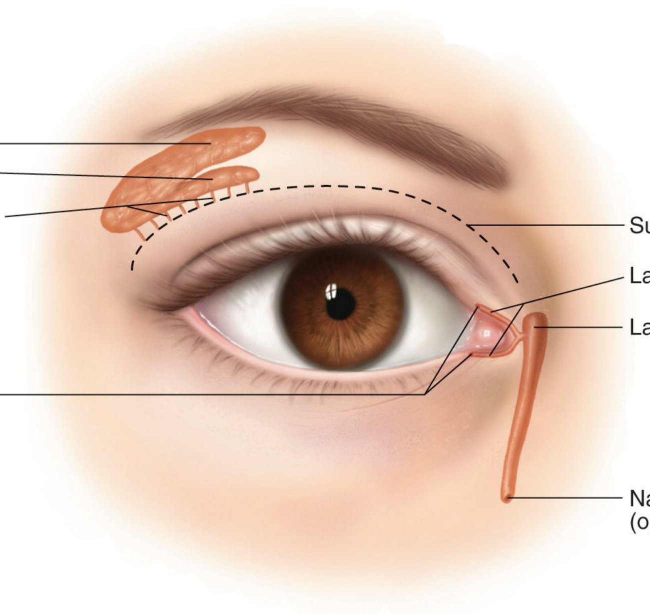


Figure 10.11. Anatomy of the lacrimal system. (From Pansky B, Gest TR, eds. *Lippincott's Concise Illustrated Anatomy: Head and Neck*. Vol. 3. Philadelphia, PA: Wolters Kluwer Health; 2014.)

The skin of the *eyelid* is continuous with the palpebral and bulbar conjunctivae, which are, in turn, contiguous with the globe. Each of these epithelial surfaces represents a potential site of origin for cancer.

ETIOLOGY

The cause of sinonasal neoplasms is unknown. There is some epidemiologic evidence, however, to support an occupational risk for developing cancer of the sinonasal tract (SNT).[1] Occupational exposure to inhalation of certain metal dusts or aerosols can cause loss of olfactory acuity, atrophy of the nasal mucosa, mucosal ulcers, perforated nasal septum, dysplasia of the nasal mucosa, or sinonasal cancer.[2] Cancer of the nose and paranasal sinuses has been reported to be more frequent in workers exposed to nickel compounds in nickel refining, cutlery factories, and alkaline battery manufacture or to chromium in chromate production and chrome plating.[3] In a report on the risk of developing sinonasal cancer in Scandinavian countries, nickel workers involved with electrolytic work for more than 15 years were found to have a 250-fold increased incidence of cancer of the sinus. In the same study, random biopsy of the middle turbinate showed evidence of dysplasia in 21%

of workers. These changes were independent of their smoking history. All workers had been employed for at least 10 years, and there was an average latent period of 18 to 36 years before the development of carcinoma, most of which were squamous cell or anaplastic.[4] Similarly, in a Swedish cohort of workers (n = 6,454) from seven aluminum foundries and three secondary aluminum (scrap) smelters, significantly elevated risk estimates for sinonasal cancer were observed.[5]

In animals, several heavy metals (e.g., Al, Cd, Co, Hg, Mn, Ni, Zn) have been shown to pass via olfactory receptor neurons from the nasal lumen through the cribriform plate to the olfactory bulb. Some metals (e.g., Mn, Ni, Zn) can even cross synapses in the olfactory bulb and migrate via secondary olfactory neurons to distant nuclei of the brain. The olfactory bulb tends to accumulate certain metals (e.g., Al, Bi, Cu, Mn, Zn) with greater avidity than other regions of the brain. The molecular mechanisms responsible for metal translocation in olfactory neurons and deposition in the olfactory bulb are unclear, but chelation by metal-binding molecules such as carnosine (beta-alanyl-L-histidine) may be involved.[3]

Other occupational exposures may also increase the risk of developing cancer of the SNT.[6] A European case–control study revealed that exposure to leather and wood dust was associated with an excess risk of sinonasal cancer.[7] Both wood and leather dusts were associated more with adenocarcinoma than SCC.[6,8] Recent large-scale studies suggest that this increased risk is specifically linked to the development of intestinal-type adenocarcinoma rather than other types of sinonasal adenocarcinomas (SNACs).[9–11] In European populations, occupation was associated with about 11% of all sinonasal cancers in women and 39% in men. A meta-analysis of 12 large case–control studies estimated that male wood workers had a summary odds ratio of sinonasal cancer of 2.6 (95% confidence interval [CI] = 2.1 to 3.3).[12] The risk was greatest among men who had been employed in jobs with the highest wood dust exposure and increased with duration of exposure.[13] Employment in the boot and shoe industry has been also associated with adenocarcinoma of the nasal cavity in England and Italy.[14] Data from a case–control study conducted at 27 hospitals in France showed exposure to textile dust were associated with an elevated risk of SCC and adenocarcinoma of the SNT and that the risk increased with the duration

and the level of exposure.[15]

Although epidemiologic studies have not addressed the relationship between outdoor air pollution and sinonasal malignant neoplasms, a report on the incidence of sinonasal cancer in urban polluted cities suggests such a correlation.[16] Both primary and environmental (secondary) tobacco smoke appear to be also related to increase in the incidence of sinonasal cancer, particularly sinonasal squamous cell carcinoma (SNSCC).[7,17,18] Recent studies have found a correlation in the development of lung cancer and SNSCC, propagating a possible causal relationship between SNSCC and smoking.[19]

High-risk human papillomavirus (HR-HPV) is an established cause of head and neck carcinomas arising in the oropharynx. The presence of HPV has also been reported in some carcinomas arising in the SNT, but little is known about their overall incidence or their clinicopathologic profile. In a recent study by Takahashi et al.[20] of 70 patients with SNSCCs treated with surgery between 1999 and 2009 at MD Anderson Cancer Center (MDACC), high-risk HPV and its surrogate p16 were found in only 10% and 18% of tumor tissues, respectively. However, Bishop et al.[21] reported higher prevalence rates of both high-risk HPV and p16 in sinonasal cancers. Of 161 sinonasal carcinomas, 34 (21%) were positive for HR-HPV DNA, including type 16 (82%), type 31/33 (12%), and type 18 (6%). Immunohistochemistry for p16 was positive in 59/161 (37%) cases, and p16 expression strongly correlated with the presence of HPV DNA: 33 of 34 (97%) HPV-positive tumors exhibited high p16 expression, whereas only 26 of 127 (20%) HPV-negative tumors were p16 positive ($p < 0.0001$). A trend toward improved survival was observed in the HPV-positive group (hazard ratio [HR] = 0.58, 95% CI [0.26, 1.28]). The presence of HR-HPV in 21% of sinonasal carcinomas suggests that HPV may be an important oncologic agent of carcinomas arising in the SNT. Although nonkeratinizing SCC is the most common histologic type, there is a wide morphologic spectrum of HPV-related disease that includes a variant that resembles adenoid cystic carcinoma (ACC). The distinctiveness of these HPV-related carcinomas of the SNT with respect to risk factors, clinical behavior, and response to therapy remains to be clarified.[21]

PATHOLOGY

The mucosal lining of the nose—*the schneiderian membrane*—is derived from ectoderm. This is uniquely different from the mucosa of the rest of the upper respiratory tract, which is derived from endoderm. Olfactory neuroepithelium lines the superior portion of the nasal cavity and the roof of the nose and gives rise to neuroectodermal tumors such as olfactory neuroblastoma and neuroendocrine carcinoma (NEC).[22–24] The sinonasal epithelium also has minor salivary glands (SGs) and gives rise to SG tumors such as ACC and mucoepidermoid carcinoma (MEC).[25–28] However, the most common epithelial neoplasms of the SNT are those arising from "metaplastic" squamous epithelium namely SCC and those originating from the seromucinous glands of the mucosal lining, collectively known as adenocarcinomas.[29] The unique histology of this region is reflected in the histogenesis of a complex variety of epithelial and nonepithelial tumors (**Table 10.1**). These tumors have a wide range of biologic behavior, and a few arise only in the SNT (e.g., inverted papilloma, olfactory neuroblastoma). Nonepithelial tumors are similar to those in other regions in the head and neck.

Table 10.1 Tumors of the Sinonasal Tract

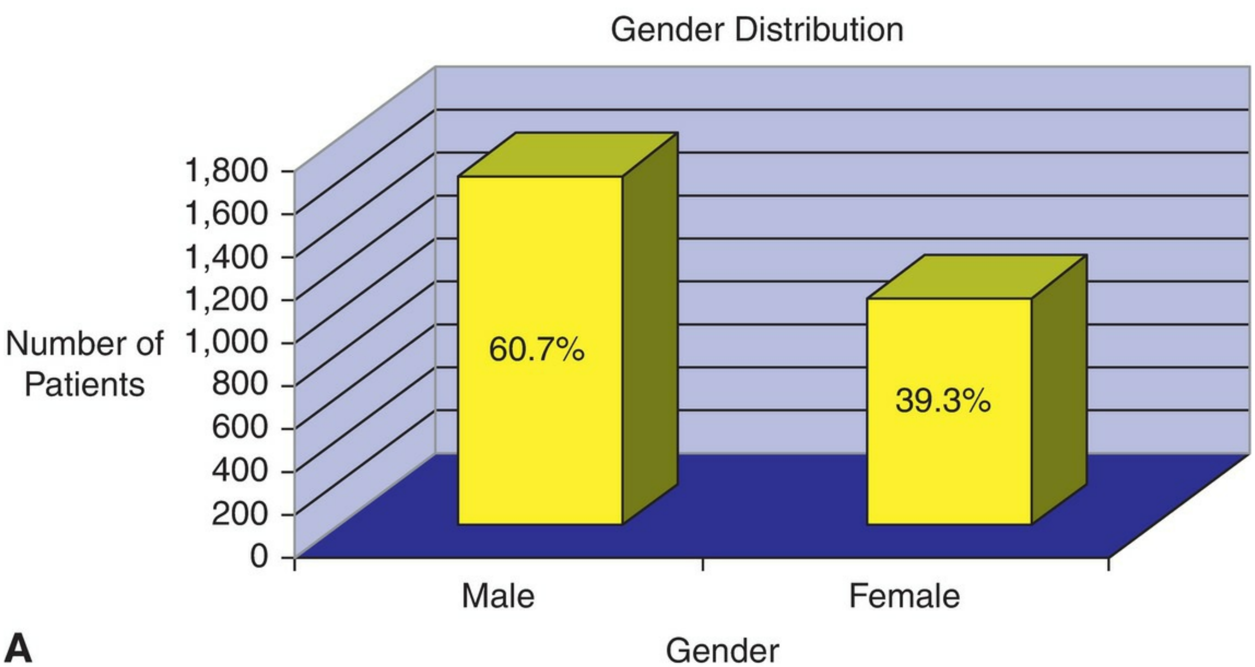
Benign
- Epithelial
  - Papilloma
  - Adenoma
  - Dermoid
- Nonepithelial
  - Fibroma
  - Chondroma
  - Osteoma
  - Neurofibroma
  - Hemangioma
  - Lymphangioma
  - Nasal glioma

Intermediate
- Schneiderian papilloma
  - Inverted
  - Papillary
  - Cylindrical
- Angiofibroma
- Ameloblastoma
- Fibrous dysplasia
- Ossifying fibroma
- Giant cell tumor

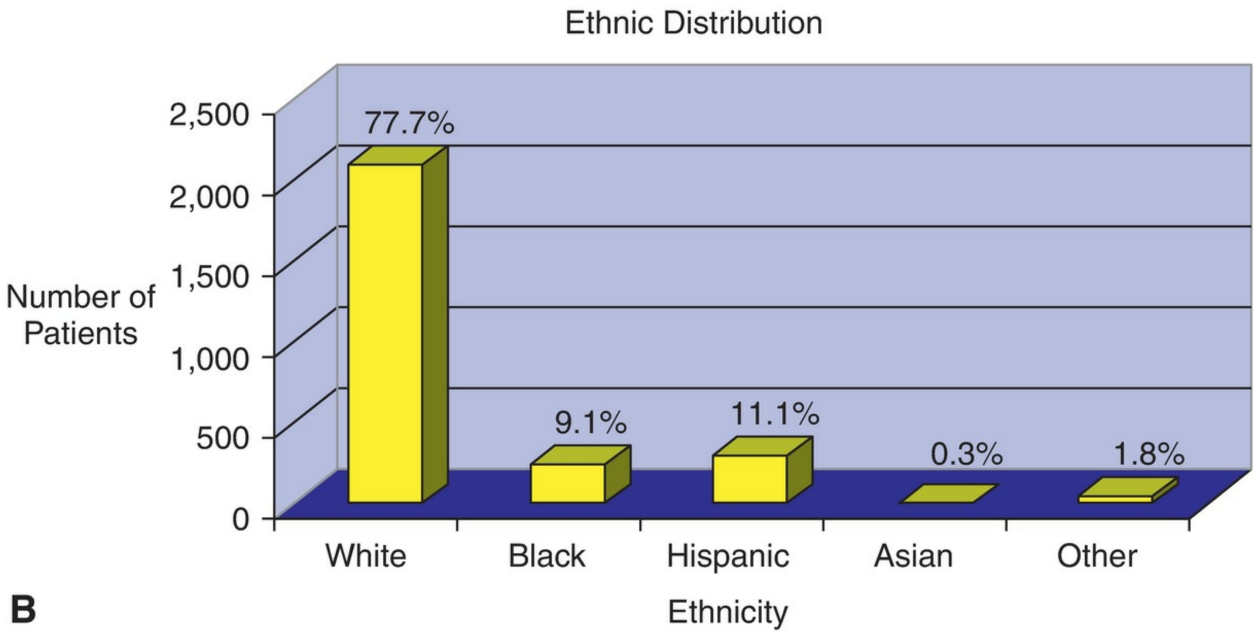
Malignant
- Epithelial
  - Squamous cell carcinoma
    - Differentiated (well, moderately, poorly)
    - Basaloid squamous
    - Adenosquamous
  - Nonsquamous cell carcinoma
    - Adenoid cystic carcinoma
    - Mucoepidermoid carcinoma
    - Adenocarcinoma
    - Neuroendocrine carcinoma
    - Hyalinizing clear cell carcinoma
  - Melanoma
  - Olfactory neuroblastoma
  - Sinonasal undifferentiated carcinoma (SNUC)
- Nonepithelial
  - Chondrosarcoma
  - Osteogenic sarcoma
  - Chordoma
  - Soft tissue sarcoma
    - Fibrosarcoma
    - Malignant fibrous histiocytoma
    - Hemangiopericytoma
    - Angiosarcoma
    - Kaposi sarcoma
    - Rhabdomyosarcoma
  - Lymphoproliferative
    - Lymphoma
    - Polymorphic reticulosis
    - Plasmacytoma
- Metastatic
  - Renal
  - Lung
  - Breast
  - Ovary

INCIDENCE

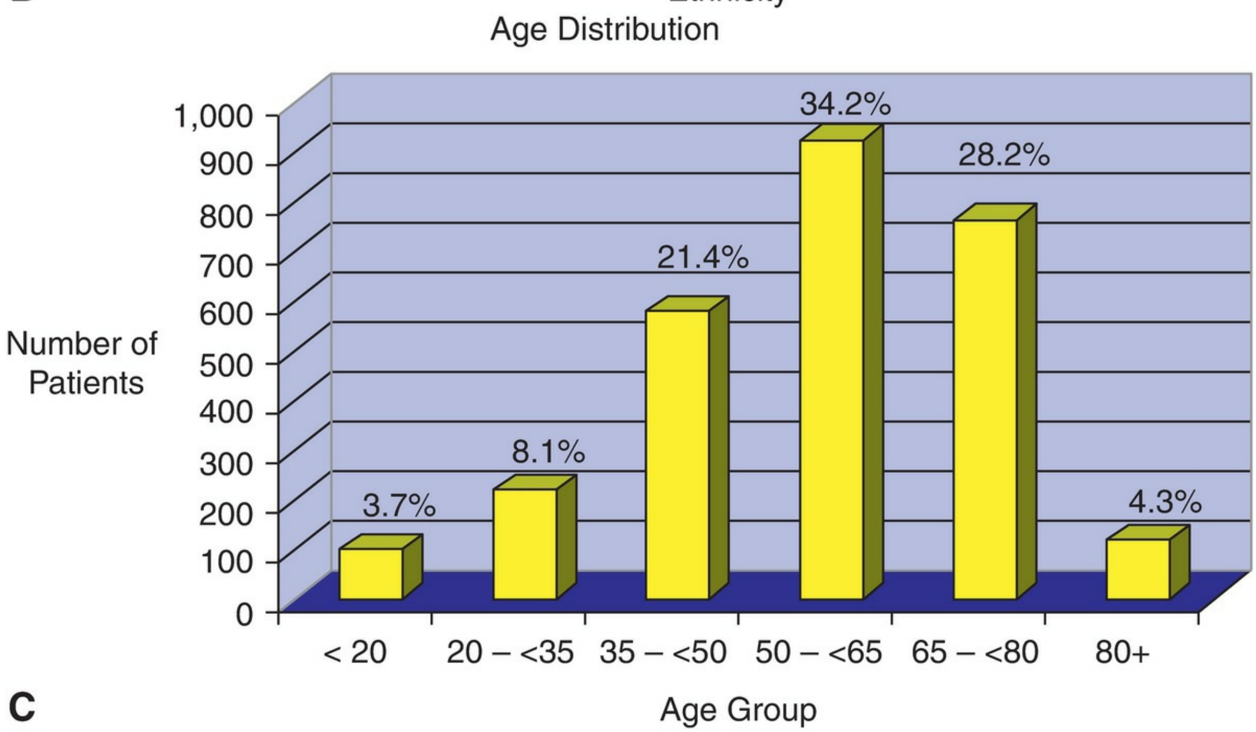
Overall, sinonasal cancer accounts for about 1% of all malignancies and ~3% of cancer of the head and neck. There is a male predominance (**Fig. 10.12A**), with a strong predilection for Caucasians (**Fig. 10.12B**). The majority of patients are over 50 years of age at the time of diagnosis (**Fig. 10.12C**). The most common malignant tumor of the nasal cavity and paranasal sinuses is SCC (**Fig. 10.12D**). Although the maxillary antrum is the most commonly involved sinus (**Fig. 10.12E**), anterior skull base invasion is most frequently encountered with malignant neoplasms of the nasal cavity and ethmoid sinus. Upward extension of these neoplasms toward the cribriform plate or fovea ethmoidalis is not uncommon and heralds intracranial extension.[30] Primary carcinoma of the frontal sinus is uncommon, and those arising in the sphenoid sinus are rare.[31] Unfortunately, despite significant improvement in diagnostic techniques such as nasal endoscopy and high-resolution imaging, most patients present with advanced stage disease (**Fig. 10.12F**).



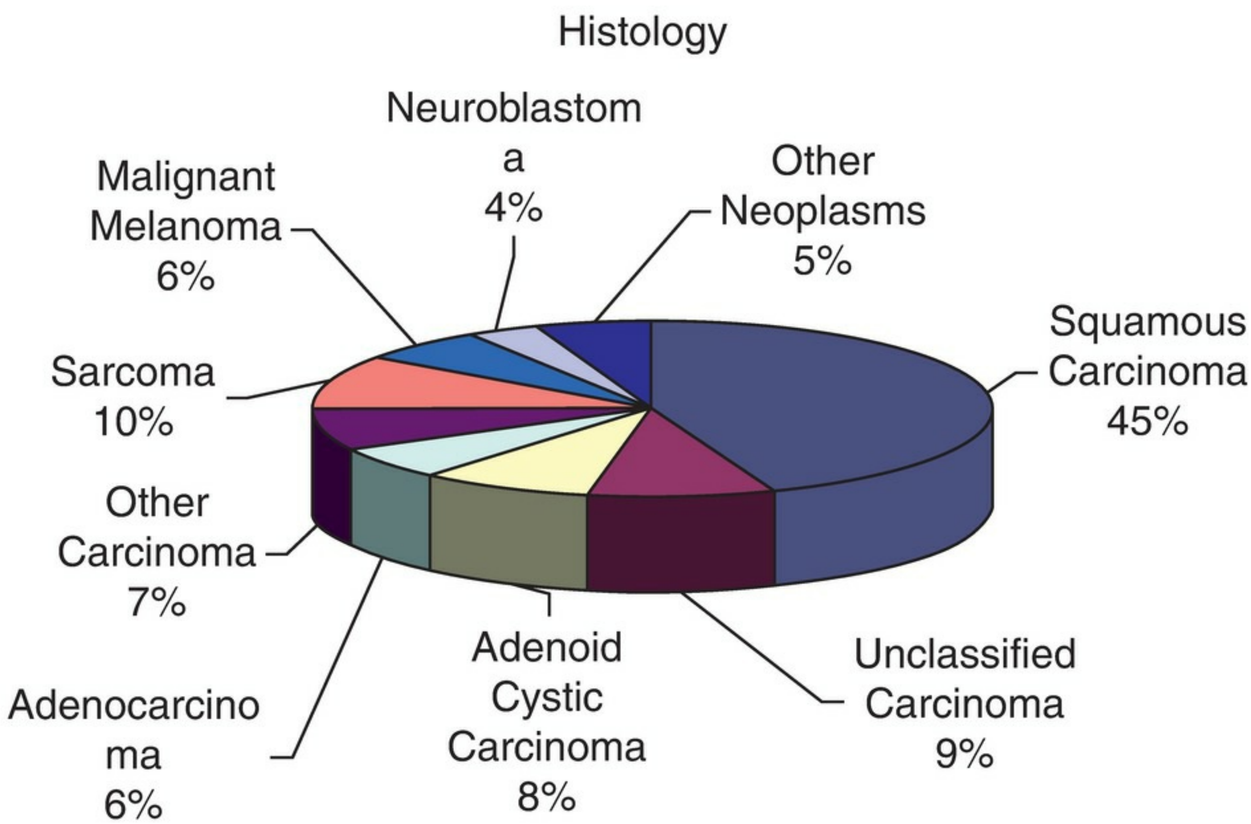
A


Ethnic Distribution
Number of Patients
2,500
2,000
1,500
1,000
500
0
77.7%
9.1%
11.1%
0.3%
1.8%
White
Black
Hispanic
Asian
Other
Ethnicity

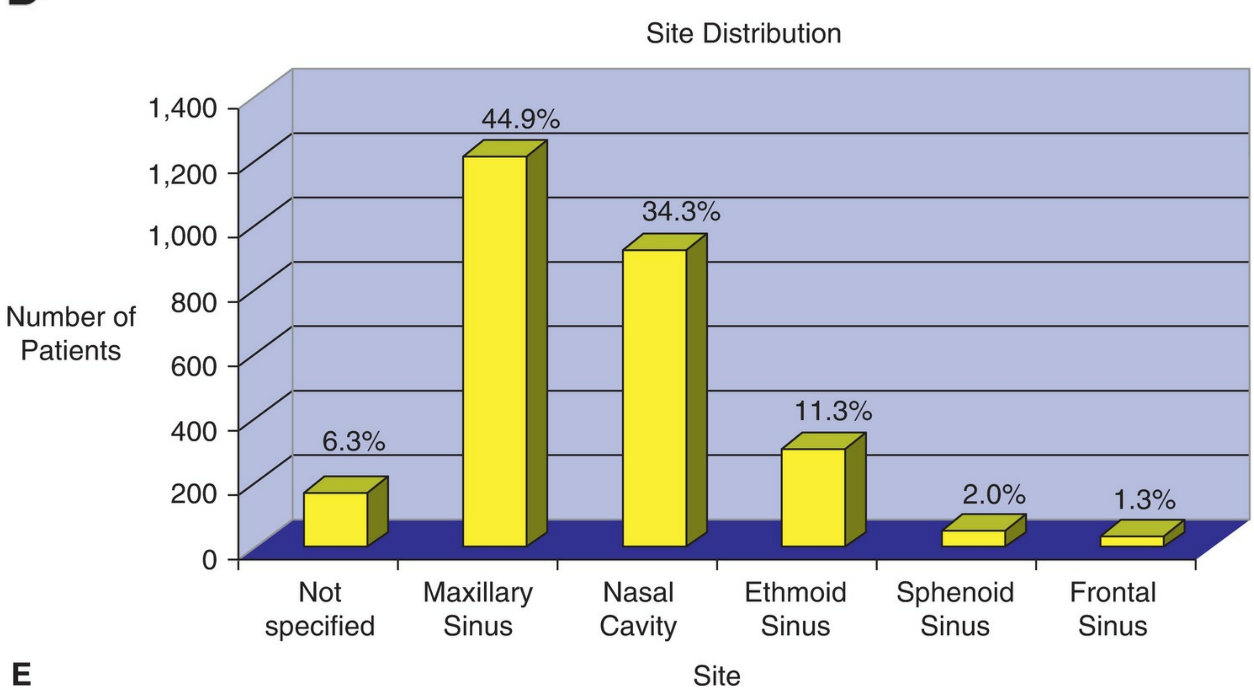
B


Age Distribution
Number of Patients
1,000
900
800
700
600
500
400
300
200
100
0
3.7%
8.1%
21.4%
34.2%
28.2%
4.3%
< 20
20 – <35
35 – <50
50 – <65
65 – <80
80+
Age Group

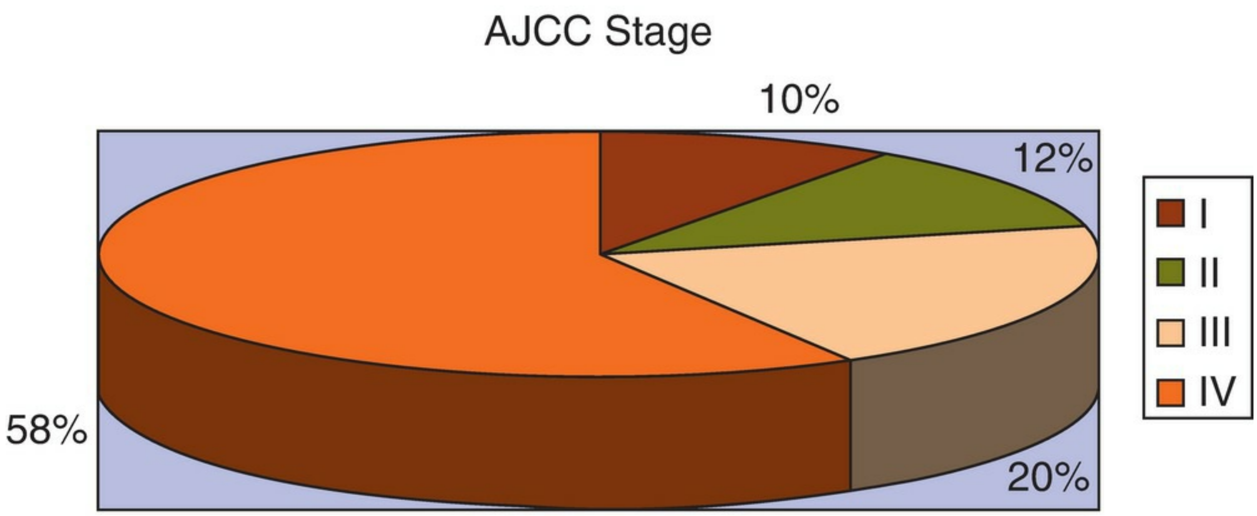
C


Histology
Neuroblastom
a
4%
Other
Neoplasms
5%
Malignant
Melanoma
6%
Squamous
Carcinoma
45%
Sarcoma
10%
Other
Carcinoma
7%
Unclassified
Carcinoma
9%
Adenoid
Cystic
Carcinoma
8%
Adenocarcino
ma
6%

D


Site Distribution
1,400
1,200
1,000
800
600
400
200
0
Number of
Patients
44.9%
34.3%
11.3%
6.3%
2.0%
1.3%
Not
specified
Maxillary
Sinus
Nasal
Cavity
Ethmoid
Sinus
Sphenoid
Sinus
Frontal
Sinus
Site

E



F

Figure 10.12. A–F: Patients with sinonasal cancer seen at MD Anderson Cancer Center between 1944 and April 2007 (n = 2,698 patients).

SPREAD

Local Spread

The most common route of local spread of cancer of the SNT is through direct extension. As most sinonasal cancers are relatively asymptomatic when small, it is often the manifestation of local spread that prompts patients to seek medical attention. In the maxillary sinus, direct extension may occur anteriorly into the soft tissues of the cheek, superiorly into the orbit with resultant proptosis and diplopia, inferiorly into the oral cavity, or posteriorly into the pterygomaxillary space where it may spread along the branches of the maxillary division of the trigeminal nerve (V2). Cancer of the frontal sinus is quite rare, but the most significant direct extension is posteriorly to the frontal lobes. Cancer of the ethmoid sinus often presents with medial extension to the orbit, superior extension to the cribriform plate, and posterior extension into the sphenoid sinus and nasopharynx. Cancers involving the sphenoid sinus may quickly become problematic because of proximity to the optic nerves, the cavernous sinus (CS), and the pituitary fossa (Fig. 10.7).

In addition to direct local extension, cancer of the paranasal sinuses can spread to nearby structures via the many fissures and foramina located in this region. Cancer of the maxillary sinus frequently erodes posteriorly into the

PPF (Fig. 10.8). Once in the PPF, the tumor may extend laterally through the pterygomaxillary fissure into the infratemporal fossa, superiorly into the orbit via the inferior orbital fissure or into the middle cranial fossa through the foramen rotundum, posteriorly into the vidian canal with extension to the petrous portion of the temporal bone, or inferiorly into the oral cavity by way of the palatine canal or the sphenopalatine foramen.

From the frontal sinus, cancer may extend into the nasal cavity through the nasofrontal duct. Cancer of the ethmoidal sinuses may also extend into the nasal cavity through the middle meatus and the sphenoethmoidal recess, posteriorly into the nasopharynx and along the eustachian tube, or inferiorly along the nasolacrimal duct (Fig. 10.3).

Perineural Spread

The dissemination of cancer cells along nerves is a frequent pathologic finding among a variety of cancers, including head and neck, upper gastrointestinal, pancreatic, and prostate carcinomas. Tumors that have a considerable propensity to disseminate along nerves are known as *neurotropic cancers*. In the head and neck, the most common tumors with a predilection to invade nerves are ACCs, followed by SCCs.[32,33] Tumors of the paranasal sinus that exhibit perineural invasion (PNI) may use this route to spread in a retrograde fashion to the skull base and even progress intracranially. Alternatively, they may spread in an antegrade fashion and along the involved nerve and its terminal branches. In either case, this neural spread makes surgical resection more complicated and achieving negative surgical margins less certain. Imaging particularly MRI is critical in determining the extent of neural spread of sinonasal cancers as will be discussed later in this chapter under the section on Imaging.[34]

Gil et al.[35] reported the incidence and pattern of neural invasion (NI) in 208 patients with cancers of the paranasal sinuses and anterior skull base. Forty-one specimens (20%) had evidence of NI. Sinonasal undifferentiated, adenoid cystic, and SCC had a high propensity for NI, whereas melanoma and sarcoma rarely invaded nerves. Intraneural invasion was found in 32% of these cases, and 34% invaded more than 1 cm distal to the tumor. NI was associated with a high rate of positive margins, maxillary origin, and previous surgical treatment ($p < 0.04$) but not with stage, orbital invasion, or dural invasion. Patients with NI were more likely to undergo adjuvant radiotherapy

($p = 0.003$), which significantly improved survival in patients with minor SG carcinomas ($p = 0.04$).

Regional Metastases

The lymphatic drainage of the posterior nasal cavities and paranasal sinuses is primarily to the retropharyngeal and lateral pharyngeal nodes at the base of the skull and then to the upper jugular lymph nodes. Cancer of the anterior nasal cavity and those that erode through the maxilla into the soft tissues of the face spread to the submandibular and upper jugular lymph nodes.

Regional metastases from paranasal sinus cancer are relatively uncommon and have been characterized to a greater extent for maxillary sinus cancer than for other paranasal sites.[36] Regional disease is evident on initial presentation in ~10% of patients, and an additional 15% of patients will develop lymph node metastasis at some point after treatment. In patients with SCC of the maxillary sinus, the risk of having lymph node metastasis on presentation correlates with extension of the primary tumor to the nasopharynx or oral cavity. The risk of developing regional metastasis after treatment correlates with local tumor recurrence. The role of elective neck dissection or radiation has yet to be defined in patients with cancer of the maxillary sinus.[37] Development of regional metastasis, however, is associated with worse prognosis.

Distant Metastases

Although distant metastasis from cancer of the paranasal sinus does occur, failure to control the disease secondary to local recurrence is far more common. For SCC of the maxillary sinus, the rate of distant metastasis is ~10% and rarely occurs in the absence of local recurrence. Cancer of the ethmoid has a similar rate of distant metastasis, with adenocarcinoma having a slightly higher rate than squamous cell cancer (15% to 20% vs. 10%). In general, the most common sites for metastasis are the lung and bone.[36–38]

STAGING

The most widely used staging system for sinonasal cancers is the American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) system.

There is a different staging system for tumors of the maxillary sinus from that used for ethmoid sinus and nasal cavity tumors. The nodal staging system for maxillary, ethmoid, and nasal cavity tumors is the same as for other sites in the head and neck and depends on the number, size, and laterality of involved lymph nodes. There is a separate staging system for esthesioneuroblastoma (ENB). The classification from the most recent version, 7th edition,[39] is shown in **Table 10.2**.

Table 10.2 Classification of Sinonasal Cancer According to the AJCC 7th Edition

Primary Tumor (T stage)		
Maxillary sinus	T1	Limited to the maxillary sinus mucosa with no erosion or bone destruction
	T2	Bone erosion/destruction including hard palate, middle nasal meatus, except for posterior wall of maxillary sinus and pterygoid plates
	T3	Invasion of bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall or orbit, pterygoid fossa, ethmoid sinuses
	T4a	Invasion of anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
	T4b	Invasion of orbital apex, dura, brain, middle cranial fossa, nasopharynx, clivus, or cranial nerves except for V2
Nasal cavity and ethmoid sinus	T1	Limited to any one subsite, with or without bony invasion
	T2	Invasion into two subsites in a single region or extending to adjacent region in the nasoethmoidal complex, with or without bony invasion
	T3	Invasion of medial wall or floor of orbit, maxillary sinus, palate or cribriform plate
	T4a	Invasion into anterior orbital contents, skin of nose or cheek, minimal extension into anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
	T4b	Invasion into orbital apex, dura, brain, middle cranial fossa, nasopharynx, clivus, or cranial nerves other than V2
Olfactory esthesioneuroblastoma	T1	Tumor isolated to nasal cavity and ethmoid sinuses
	T2	Tumor extends to sphenoid sinus or cribriform plate
	T3	Tumor extends to anterior cranial fossa or orbit, no dural invasion
	T4	Tumor invades dura or brain parenchyma
Regional Lymph Nodes (N stage)[a]		
	N0	No regional lymph node metastasis
	N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
	N2a	Metastasis in a single ipsilateral lymph node, >3 cm and ≤6 cm
	N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm
	N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm
	N3	Metastasis in a lymph node >6 cm
Distant Metastatic Disease (M stage)[b]		
	M0	No distant metastasis
	M1	Distant metastasis present

[a]Definitions apply to all subsites except for olfactory ENB, which uses a N0 vs. N1 system for positive and negative nodal metastases, respectively.

[b]Definitions apply to all subsites.

From Edge SB, et al. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010, Reference 39. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC,

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PATIENT EVALUATION

Clinical evaluation of patients with cancer of the nasal cavity, paranasal sinuses, and orbit should help to achieve three objectives: (1) establishment of the diagnosis, (2) determination of the extent of disease, and (3) development of a plan for treatment. These objectives are usually achieved through a detailed history, comprehensive clinical examination of the head and neck, imaging, and biopsy.

History and Clinical Examination

The signs and symptoms of *early* sinonasal tumors are very subtle and nonspecific. Early lesions are often completely asymptomatic or mimic more common benign conditions such as chronic sinusitis, allergy, or nasal polyposis. Since early detection of sinonasal tumors is probably the most important factor in improving prognosis, a high degree of suspicion is necessary to diagnose smaller lesions. Common symptoms include nasal obstruction, “sinus pressure” or pain, nasal discharge that may be bloody, anosmia, or epistaxis. Failure of these symptoms to respond to adequate medical therapy or the presence of unilateral signs and symptoms should alert the physician to the possibility of malignancy and warrants further investigation by high-resolution imaging. Comprehensive examination of the nasal cavity should be done after topical decongestion and anesthesia using rigid or flexible endoscopy (**Fig. 10.13**). The presence of intranasal masses, ulcers, or areas of contact bleeding may indicate a malignant tumor. Although unilateral “polyps” may be inflammatory, they are more commonly neoplastic. Tumors may also present as submucosal masses without changes in the mucosa, other than displacement. Any suspicious lesions should be biopsied, preferably after high-resolution imaging has been obtained to avoid severe bleeding and/or CSF leak as discussed below.

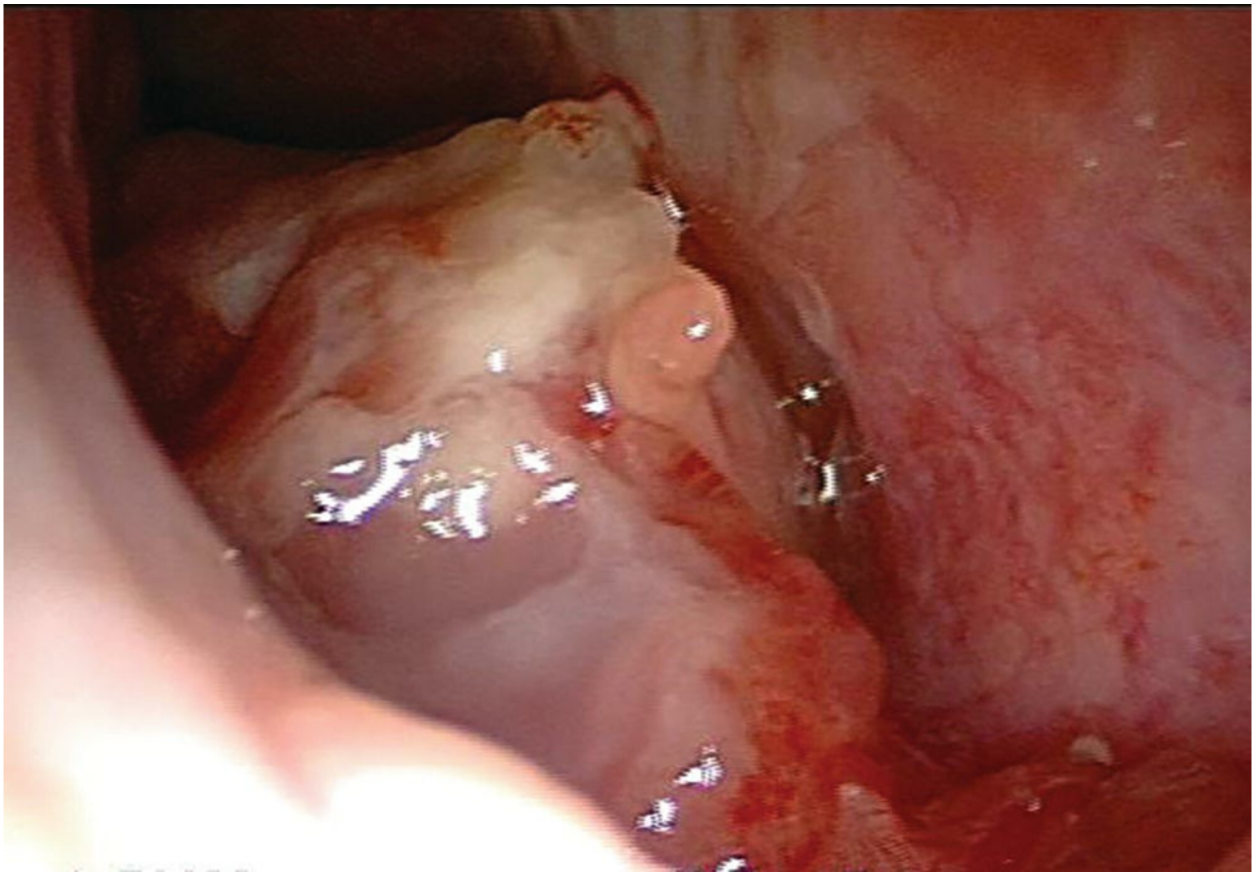

Figure 10.13. Carcinoma of the nasal cavity. Endoscopic view showing a tumor arising from the floor of the right nasal cavity. Biopsy revealed SCC.

Extension of sinonasal tumors to adjacent structures renders the diagnosis obvious, but is a late manifestation of the disease. Soft tissue swelling of the face may indicate tumor extension through the anterior bony confines of the nose and sinuses (**Fig. 10.14**). Inferior extension toward the oral cavity may present with an ulcer or a submucosal mass in the palate or the alveolar ridge (**Fig. 10.15**). Middle ear effusion may indicate tumor involvement of the nasopharynx, eustachian tube, pterygoid plates, or tensor veli palatini muscle. Extension to the skull base may lead to involvement of the cranial nerves leading to anosmia, blurred vision, diplopia, or in hypoesthesia along the branches of the trigeminal nerves. The presence of associated neck masses usually represents metastatic disease in the cervical lymph nodes.


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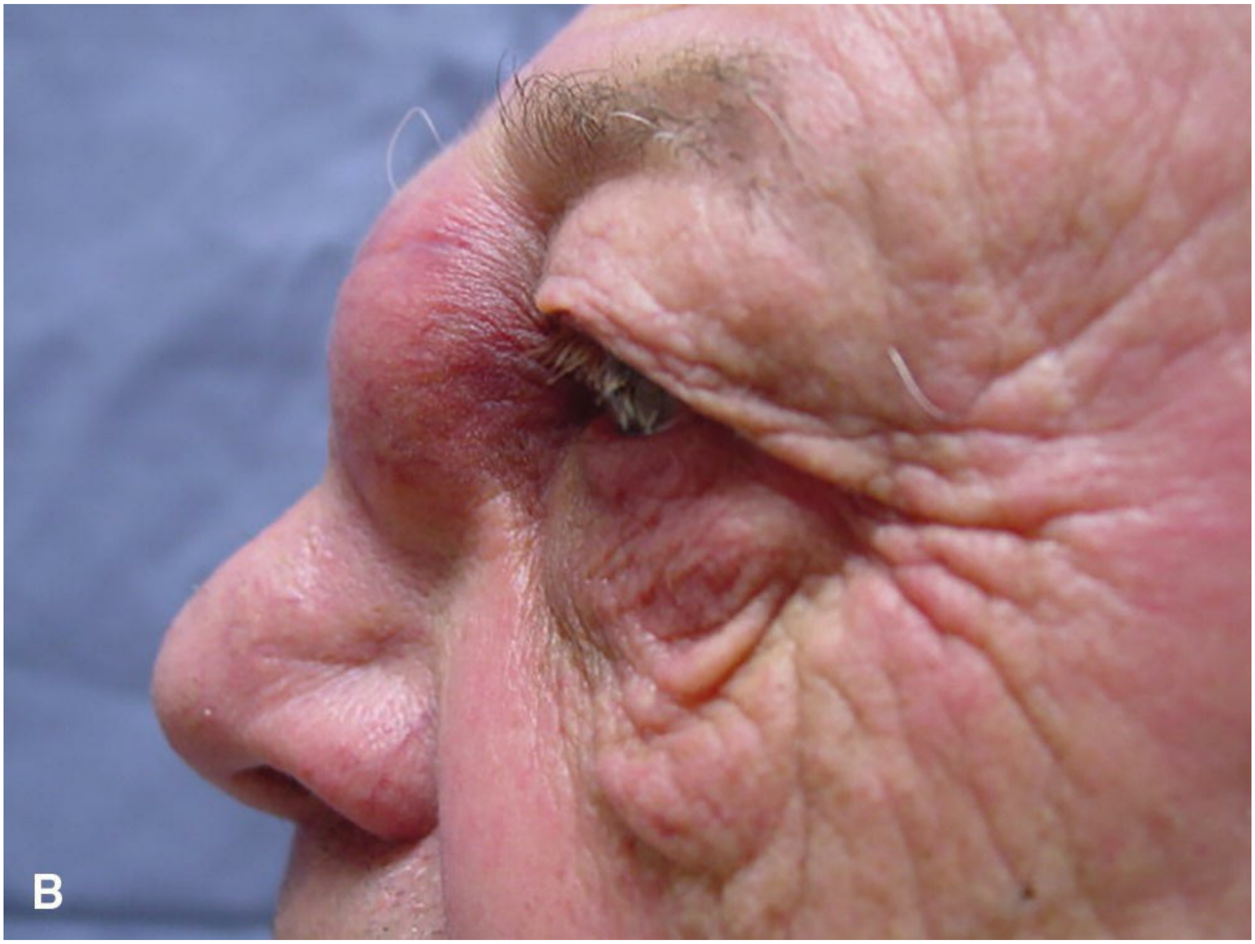


Figure 10.14. Advanced ethmoid carcinoma. **A and B:** Clinical photographs showing the mass centered on the nasion, and causing widening of the interpalpebral distance (telecanthus). The mass shows involvement of the overlying skin and destruction of the underlying nasal bone.


A

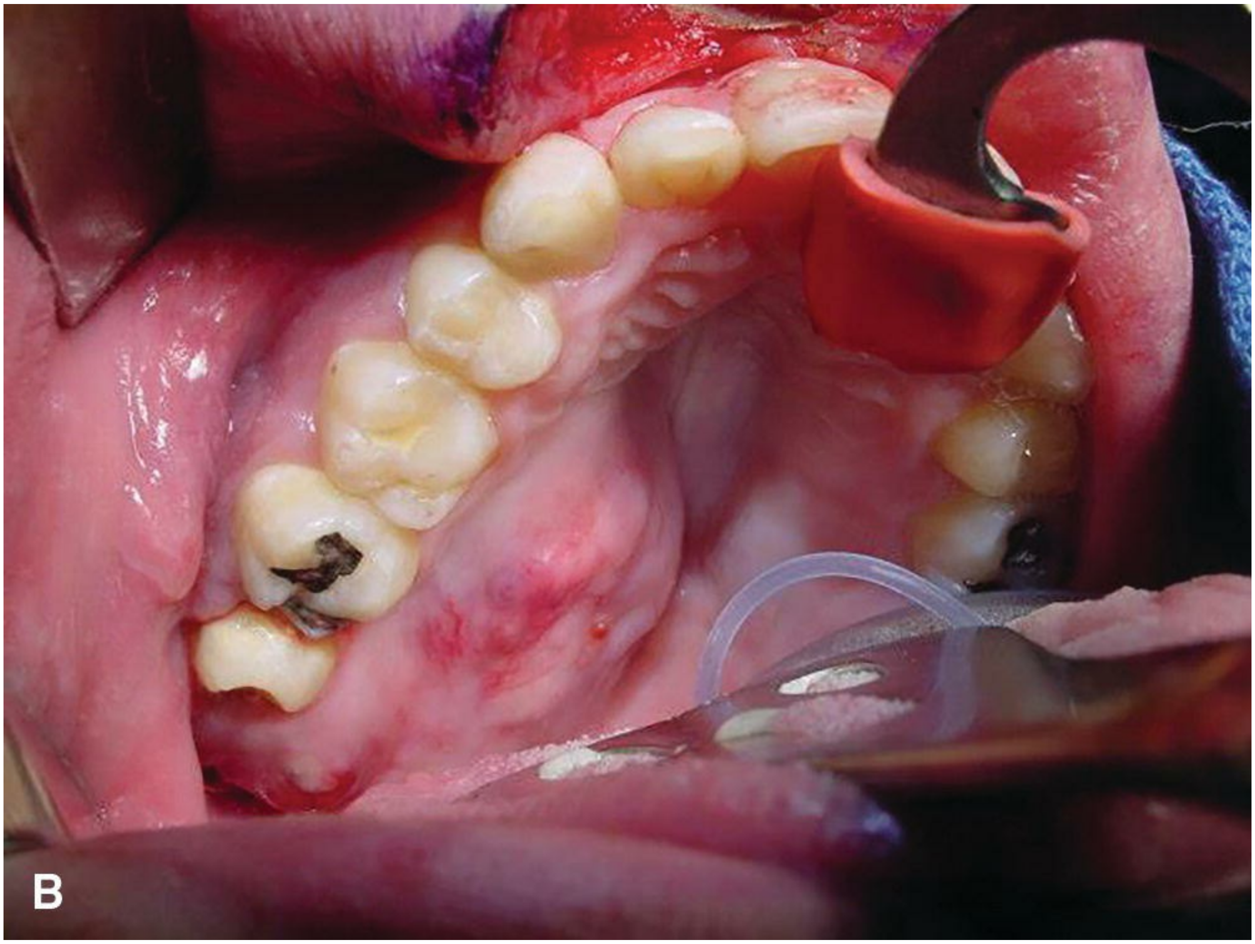


Figure 10.15. Carcinoma of the maxillary sinus may extend inferiorly and destroys the palate presenting as an ulcer **(A)** or submucosal mass **(B)**.

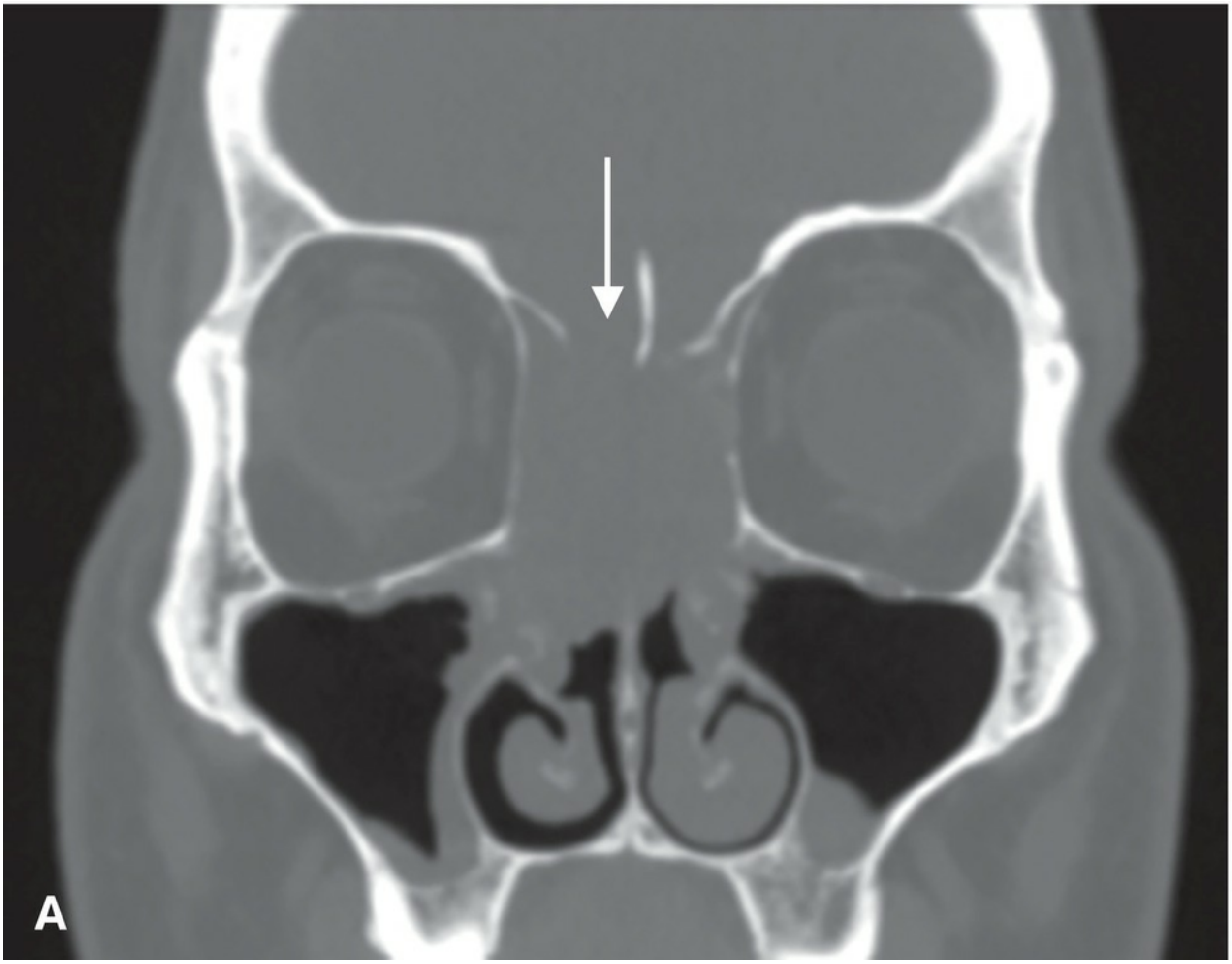
Orbital involvement is common in patients with cancer arising from the ethmoid, maxillary sinuses, frontal, and sphenoid sinuses in descending order of frequency. Less commonly, the orbit is involved by a primary tumor of the eye or its adnexa. Signs and symptoms of tumors in the orbit are usually due to mass effect or neuromuscular dysfunction. The patient may complain of proptosis, irregular shape of the eyelid, or blepharoptosis. Epiphora usually indicates involvement of the nasolacrimal duct (Fig. 10.11). Double vision may result from compression or infiltration of ocular nerves or muscles. Visual loss secondary to optic nerve involvement is usually a late sign, although more subtle signs of optic nerve dysfunction, including afferent pupillary defect, loss of color vision, and visual field defect are more frequently encountered. Finally, orbital involvement may be asymptomatic and is only discovered on computed tomography (CT) or magnetic resonance imaging (MRI) evaluation of patients with sinonasal complaints.

Evaluation of patients with suspected primary or secondary malignancy in the orbit should include a detailed neuro-ophthalmologic examination. This usually includes detailed assessment of visual acuity, visual fields, and ocular motility. Other ophthalmologic evaluation includes careful pupillary examination for afferent pupillary defect or anisocoria, external examination to include Hertel exophthalmometry, and marginal reflex distance as an indicator of eyelid position. Slit lamp examination of the conjunctivae, cornea, anterior chamber, and lens is appropriate. Finally, detailed examination of the fundus may reveal compressive effect, intraocular malignancy, or an unrelated reason for visual loss. Formal testing of color vision and automated visual fields are commonly appropriate.

Imaging

Imaging of the nasal cavity, paranasal sinuses, and orbit is indicated whenever there is clinical suspicion of a neoplastic process. Imaging is also indicated for obtaining pretreatment information regarding the location, size, extent, and invasiveness of the primary tumor, as well as the presence of regional and distant metastasis. Such information is crucial in deciding on therapeutic options and for proper preoperative planning of the optimal surgical approach. Imaging also plays an important role in the posttreatment follow-up, indicating areas of residual or recurrent disease, and defining suspicious areas for biopsy.

Both CT and MRI might be needed for optimum radiologic assessment of sinonasal malignancy, particularly in assessing the cranial base, orbit, and pterygopalatine and infratemporal fossae. Coronal images best delineate involvement of the orbital walls and invasion of the skull base, particularly the cribriform plate. Axial images are particularly helpful in demonstrating tumor extension through the posterior wall of the maxillary sinus into the PPF and infratemporal fossae. Sagittal images are particularly helpful in evaluating extension along the cribriform plate, planum sphenoidale, and clivus (**Fig. 10.16**).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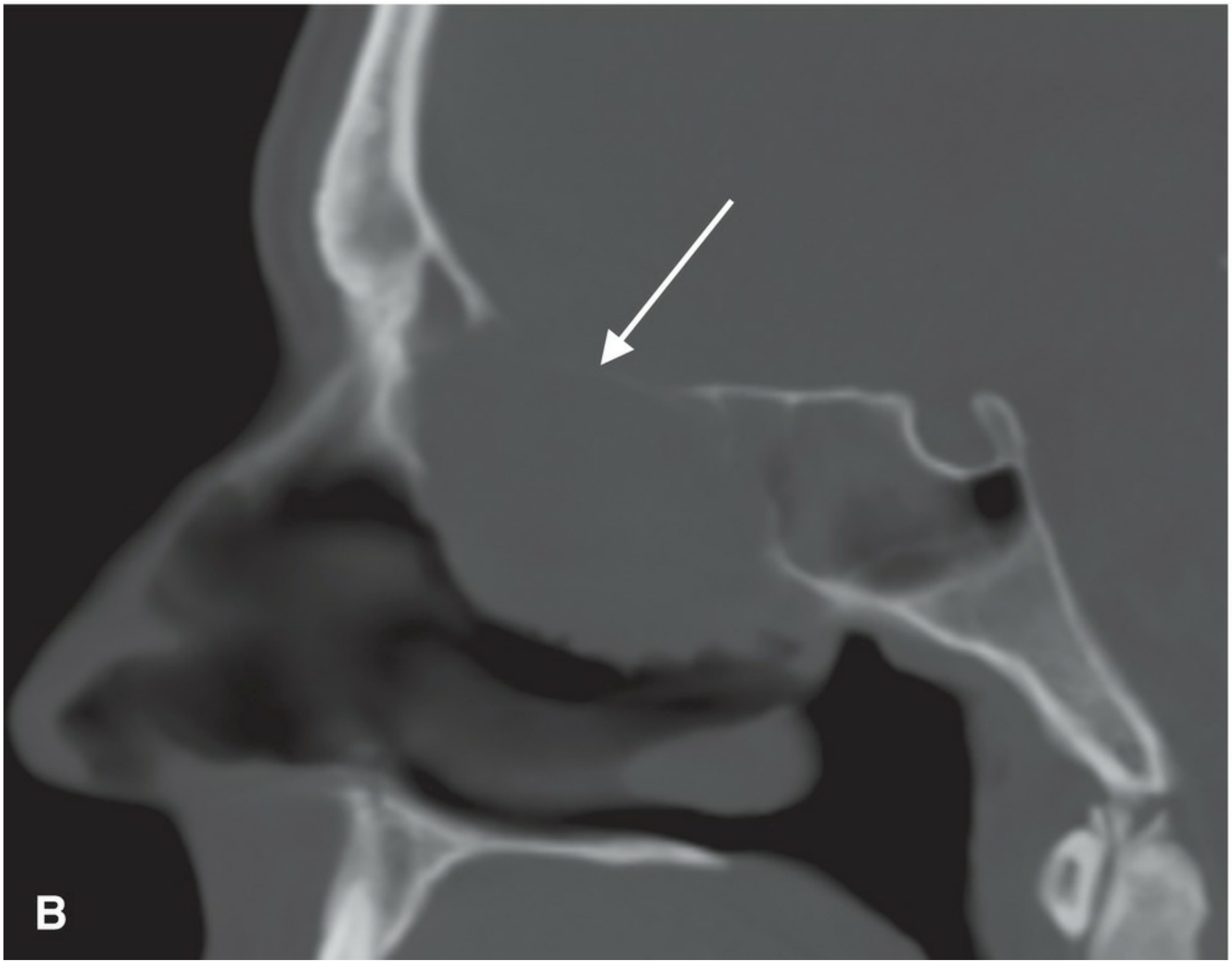
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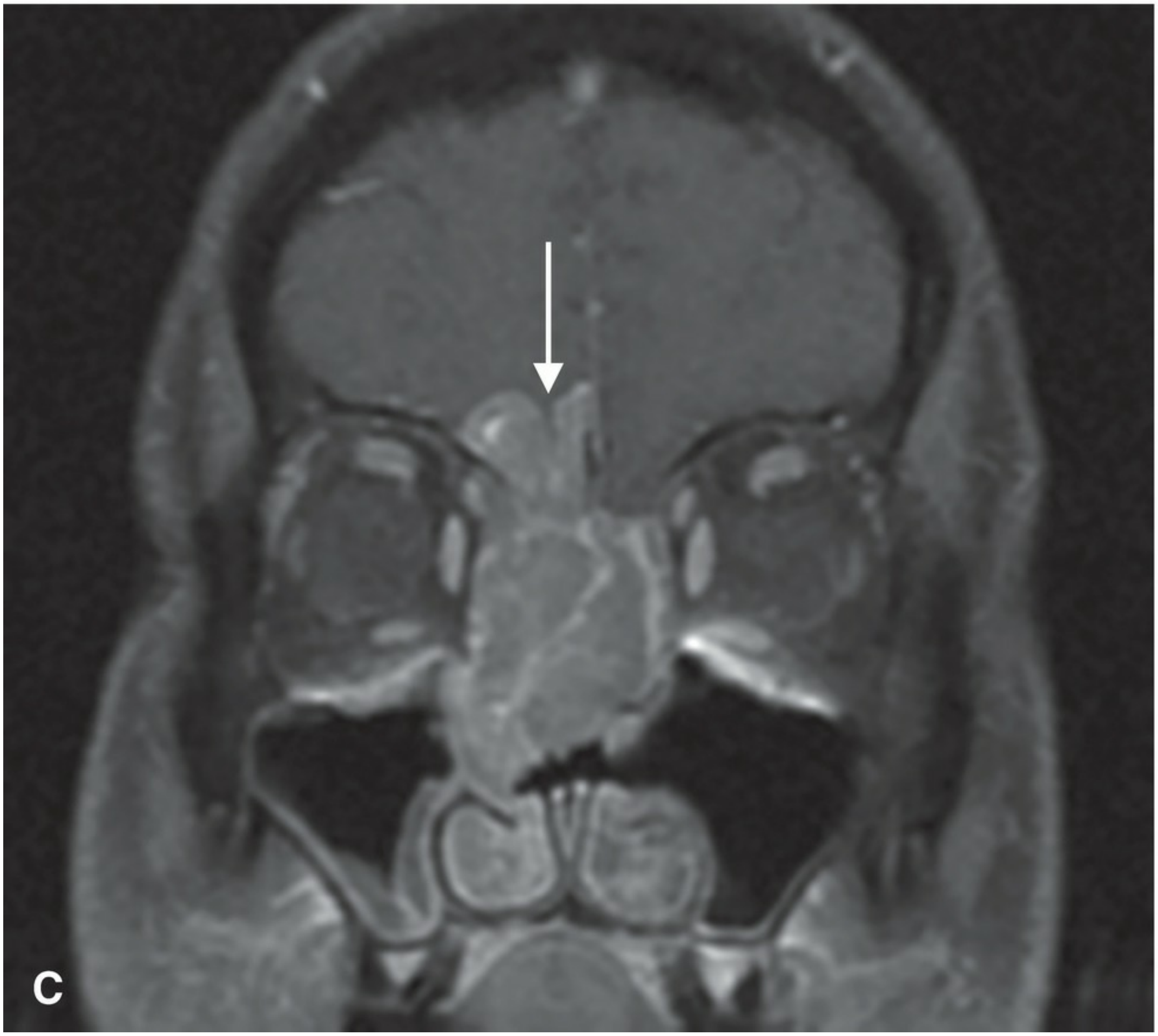
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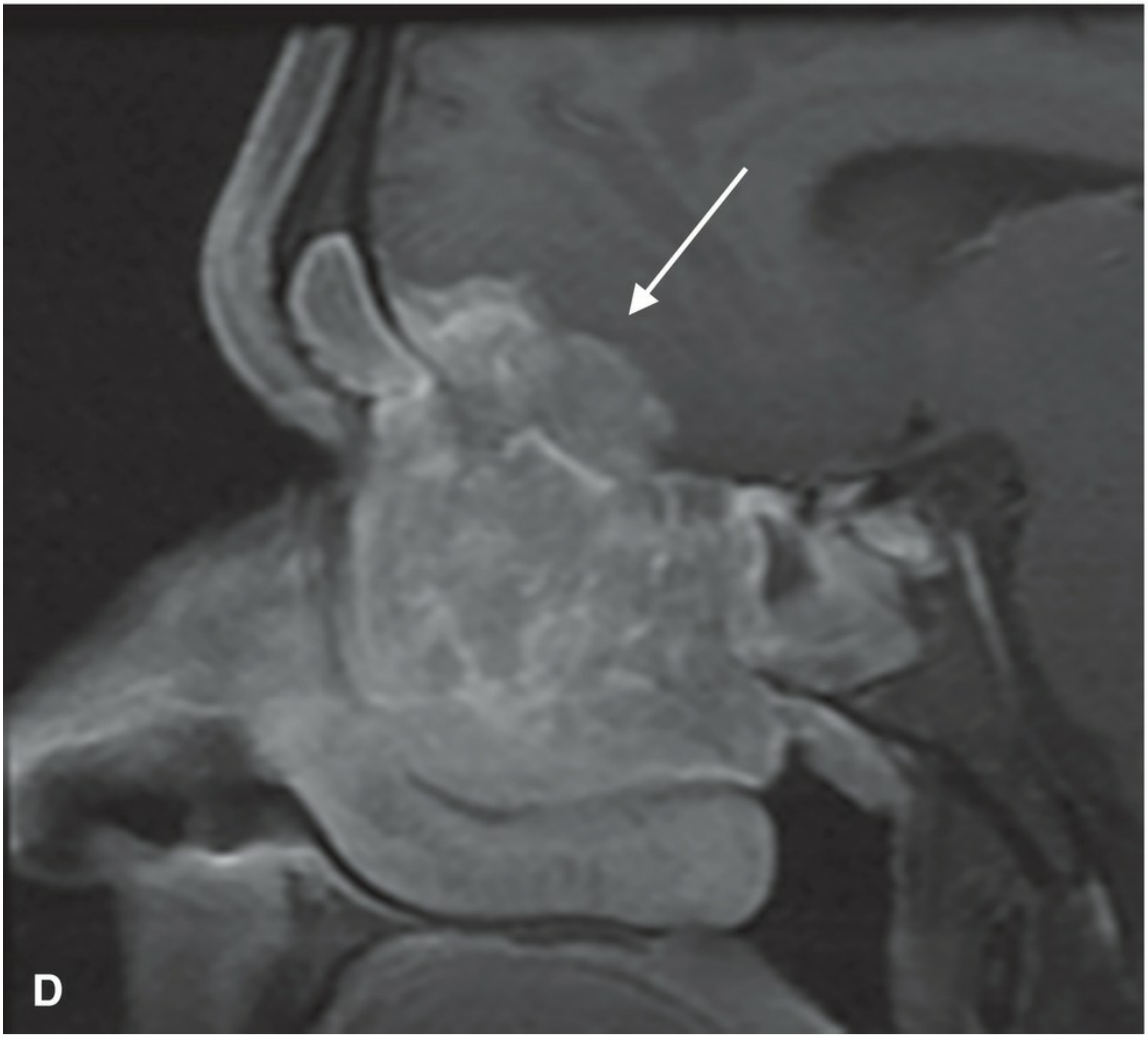
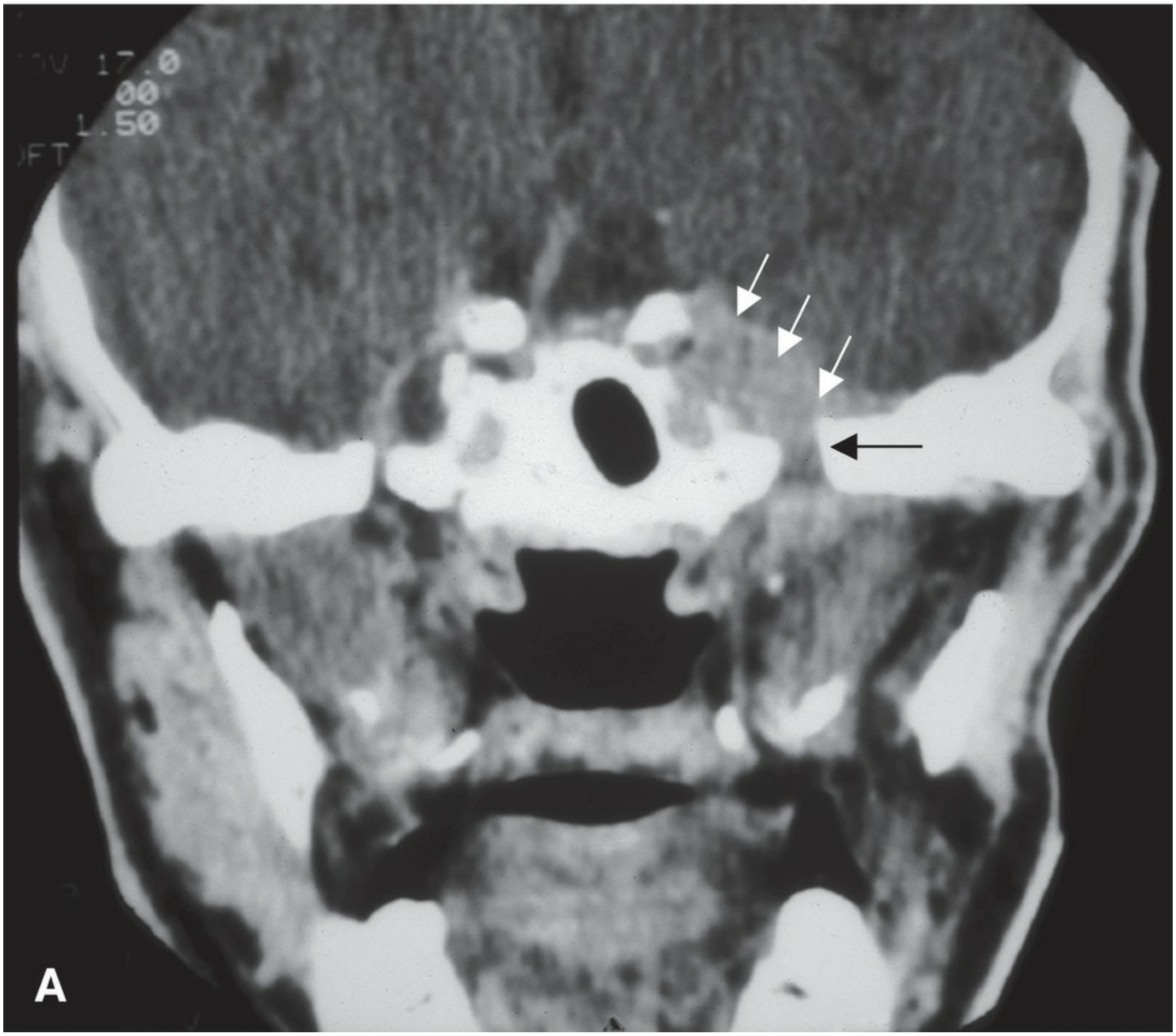


Figure 10.16. Ethmoid carcinoma. Coronal and sagittal images showing bony destruction on CT scan **(A, B)** and intracranial invasion (*arrows*) on T1-MRI with contrast **(C, D)**.

The main advantage of CT scans is in delineating the architecture of the bones, especially in "bone windows" (**Fig. 10.16A and B**). The addition of contrast enhancement increases tumor definition from adjacent soft tissue, especially intracranially. Bone destruction and soft tissue invasion suggest an aggressive lesion, usually a malignant neoplasm. Widening or sclerosis of the foramina of the infraorbital, vidian, mandibular, or maxillary nerves may indicate perineural spread (**Fig. 10.17**).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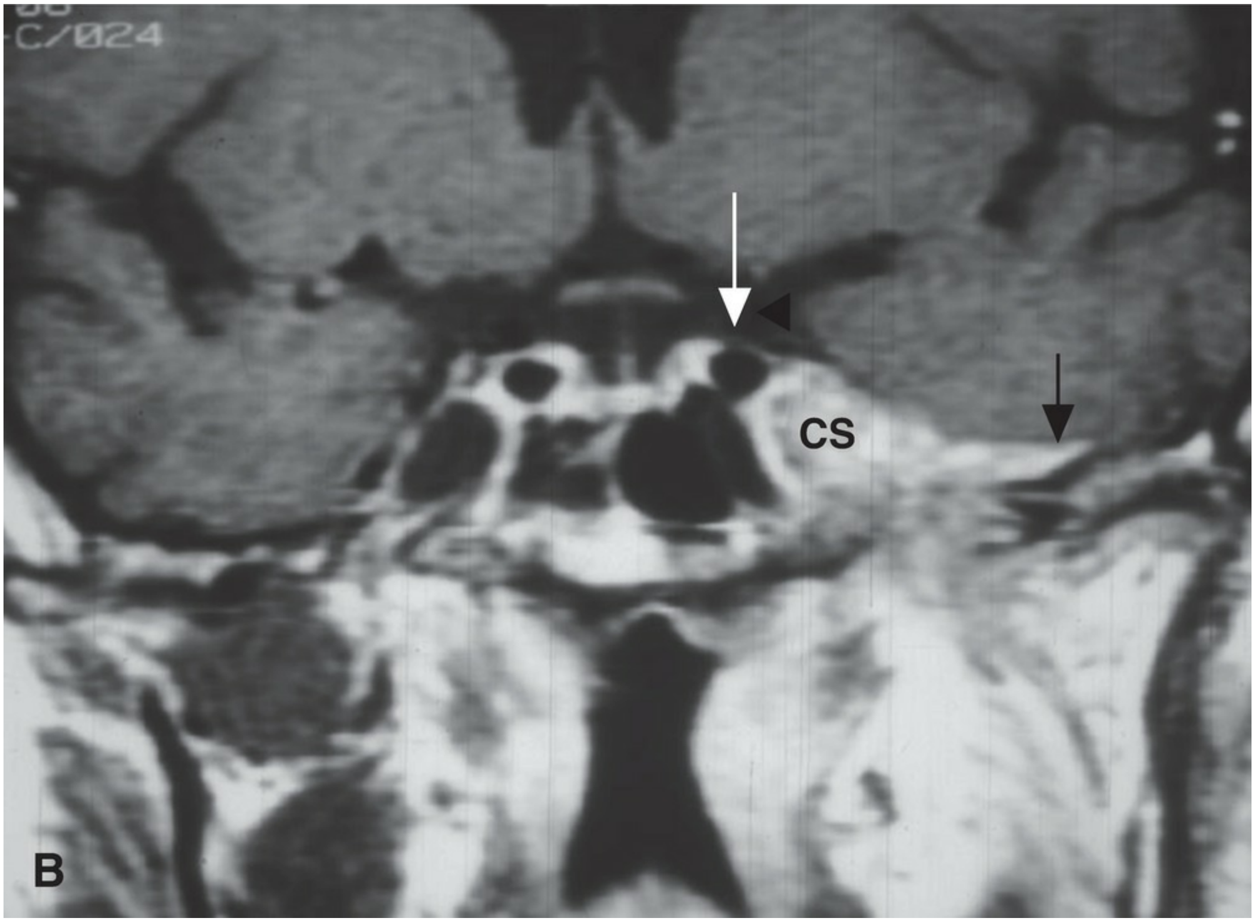
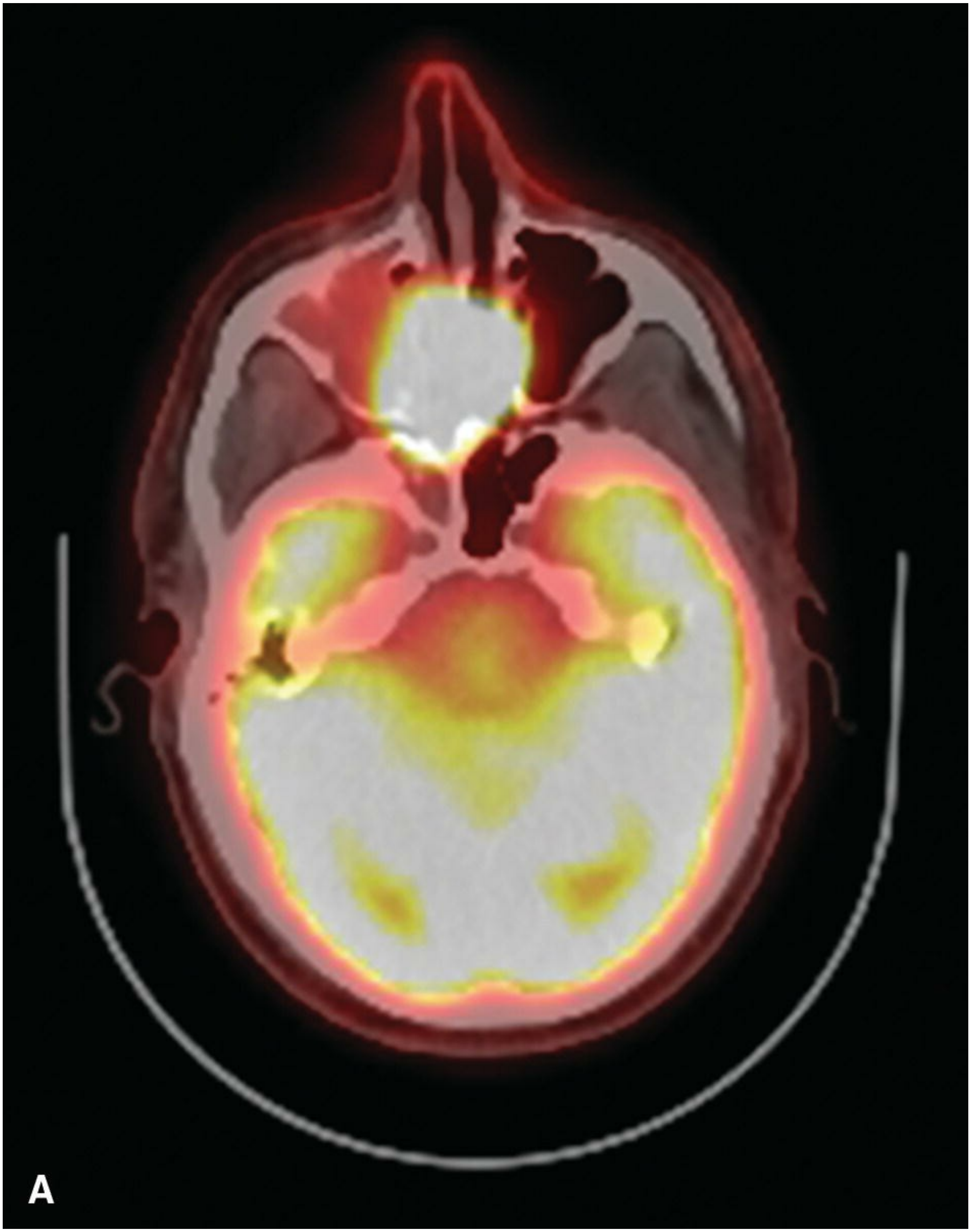


Figure 10.17. Perineural spread of ACC along the third division of the trigeminal nerve (V3). **A:** A coronal CT with IV contrast showing widening of the left foramen ovale (*black arrow*), compared to the one on the right. There is also enhancement and thickening along the left Meckel cave (*white arrows*). **B:** A coronal T1-weighted MRI with gadolinium showing marked thickening and enhancement of V3, trigeminal ganglion, and the lateral cavernous sinus (CS). The tumor abuts the cavernous carotid artery (*white arrow*). There is enhancement of the dura along the floor of the middle cranial fossa (*black arrow*). This "dural tail" is usually a sign of involvement of the dura with tumor.

MRI with its superior soft tissue contrast and multiplanar capability is superior to CT in pretreatment evaluation of primary malignant tumors of sinonasal cavity.[40] MRI is unsurpassed in delineating soft tissue detail, both intra- and extracranially (Fig. 10.16). Obliteration of fat planes in the PPF, infratemporal fossa, and nasopharynx usually indicates tumor transgression along these boundaries. Dural thickening or enhancement is usually an

indication of tumor involvement, and evaluation of critical structures such as the brain and carotid artery is best delineated by MRI. Similarly, enhancement or thickening of cranial nerves indicates perineural spread, which is better detected on MRI than CT[34] (Fig. 10.17). Perhaps one of the most significant advantages of MRI is the ability to distinguish tumor from retained secretions secondary to obstruction of sinus drainage (**Fig. 10.18**). MRI is also particularly helpful in monitoring patients in the postoperative follow-up period, although this role may be supplanted by positron emission tomography (PET) scans because of its ability to distinguish between tumor recurrence and posttreatment fibrosis. *PET–CT* is also helpful in delineating regional and distant metastasis (**Fig. 10.19**).

Figure 10.18. Sinonasal melanoma. **A:** Coronal CT scan demonstrating opacification of the right nasal cavity as well as the maxillary and ethmoid sinuses. There appears to be destruction of the lateral nasal wall and the nasal septum. The lesion is abutting the orbital floor and the cribriform plate, but it is unclear whether or not these structures are involved. **B:** Coronal T1-weighted MRI with gadolinium of the same patient revealing that the lesion is limited to the nasal cavity and ethmoid sinuses and that the changes in the maxillary sinuses are due to retained secretions secondary to obstruction of the ostium, rather than soft tissue involvement. It also demonstrates that the lesion does not invade the orbit or the cranial base. The presence of low signal areas within the lesion gives it a heterogeneous appearance, which is characteristic of sinonasal melanoma.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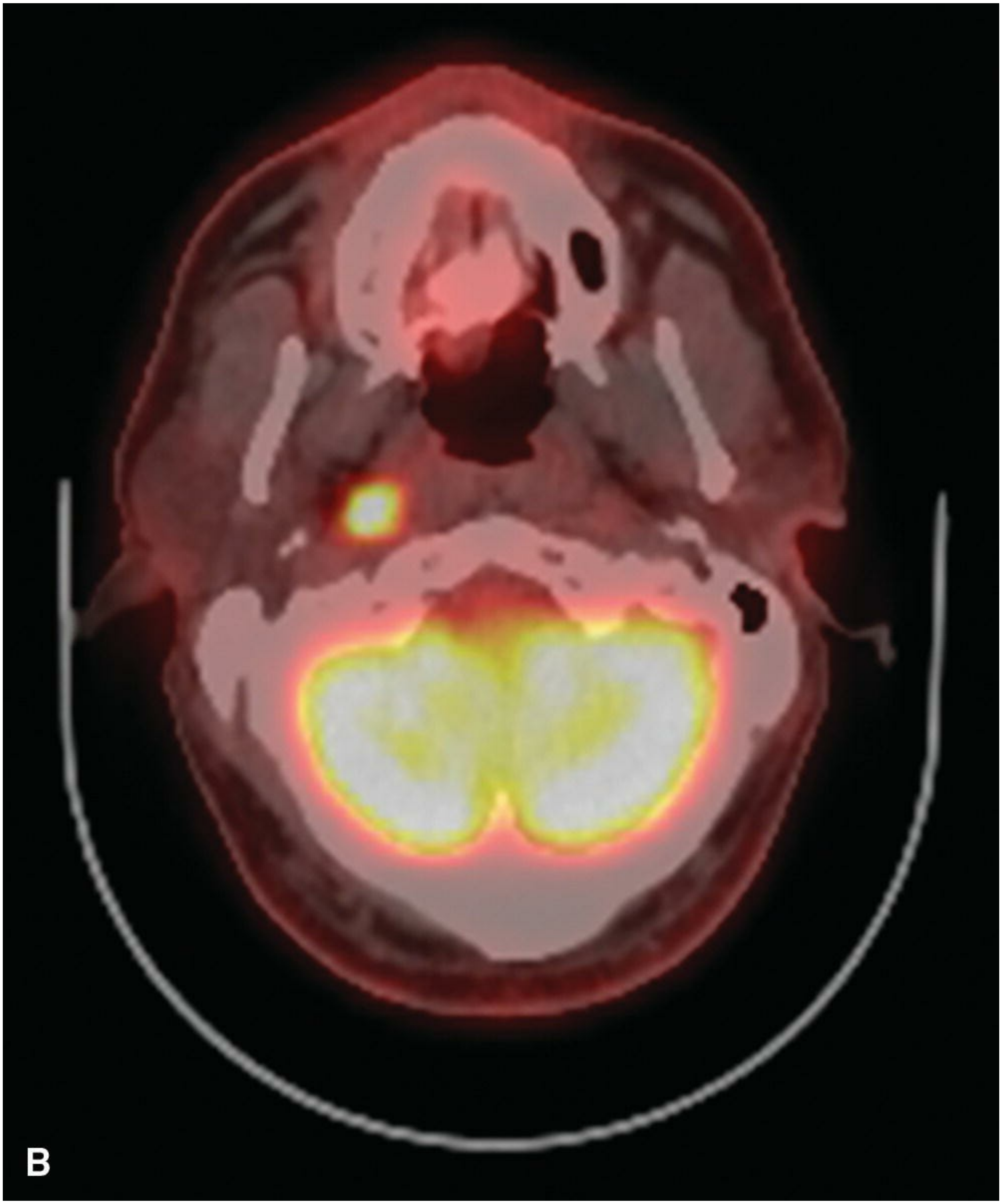
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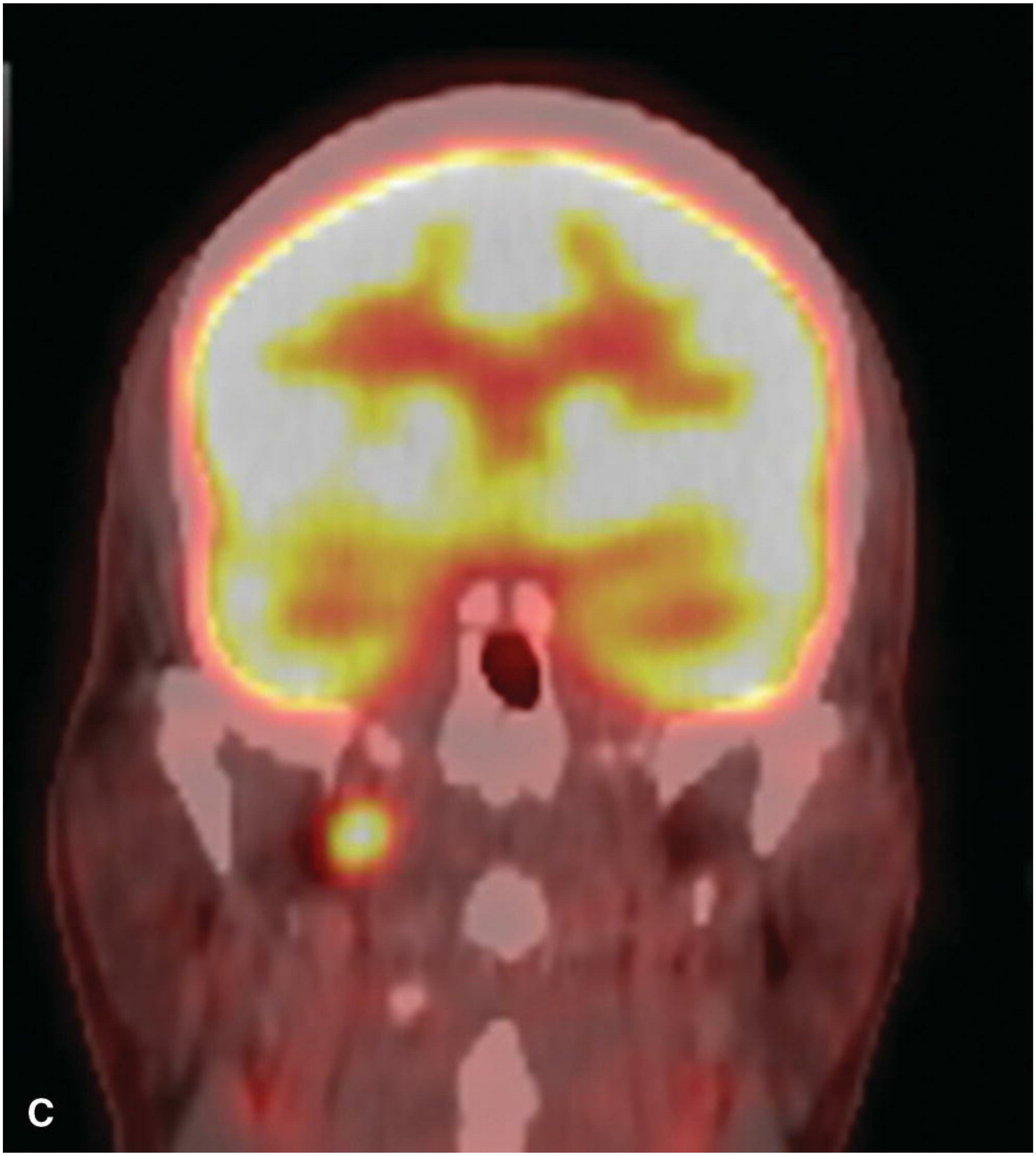
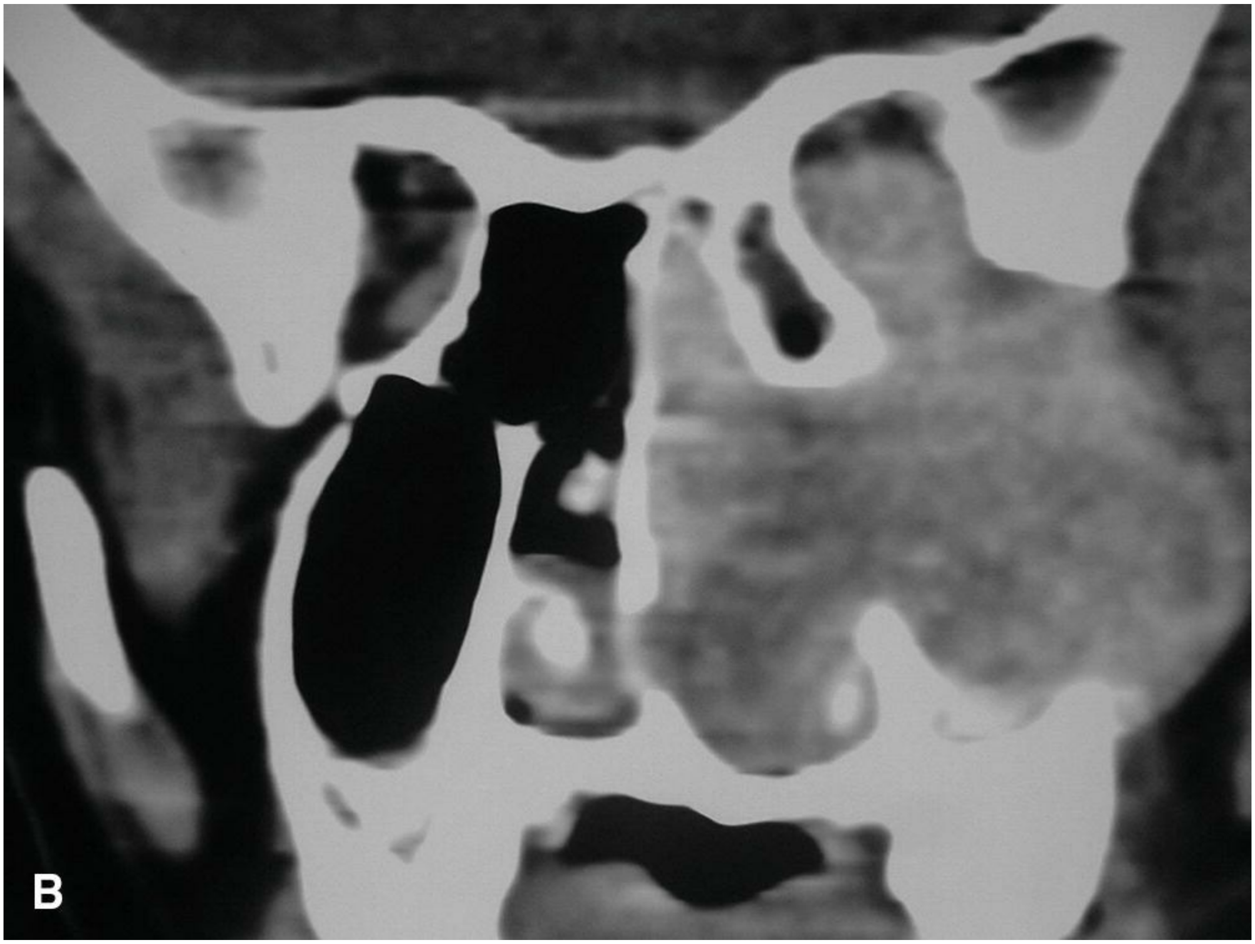


Figure 10.19. PET–CT of the head and neck. These images are from the same patient whose CT and MRI are depicted in Figure 10.16. The fused PET–CT images show ethmoid carcinoma **(A)** with metastasis to the retropharyngeal lymph nodes **(B, C)**, which were not detected on CT or MRI.

Angiography is not indicated in the routine assessment of patients with neoplasms of the nose, paranasal sinuses, and orbit. In certain selected cases,

however, angiography may be necessary. These cases include vascular neoplasms of the sinonasal region, where angiography will not only delineate the tumor extent and the blood supply but also permit the use of selective embolization of the vascular supply to the tumor (**Fig. 10.20**). This reduces intraoperative blood loss, facilitating surgical resection.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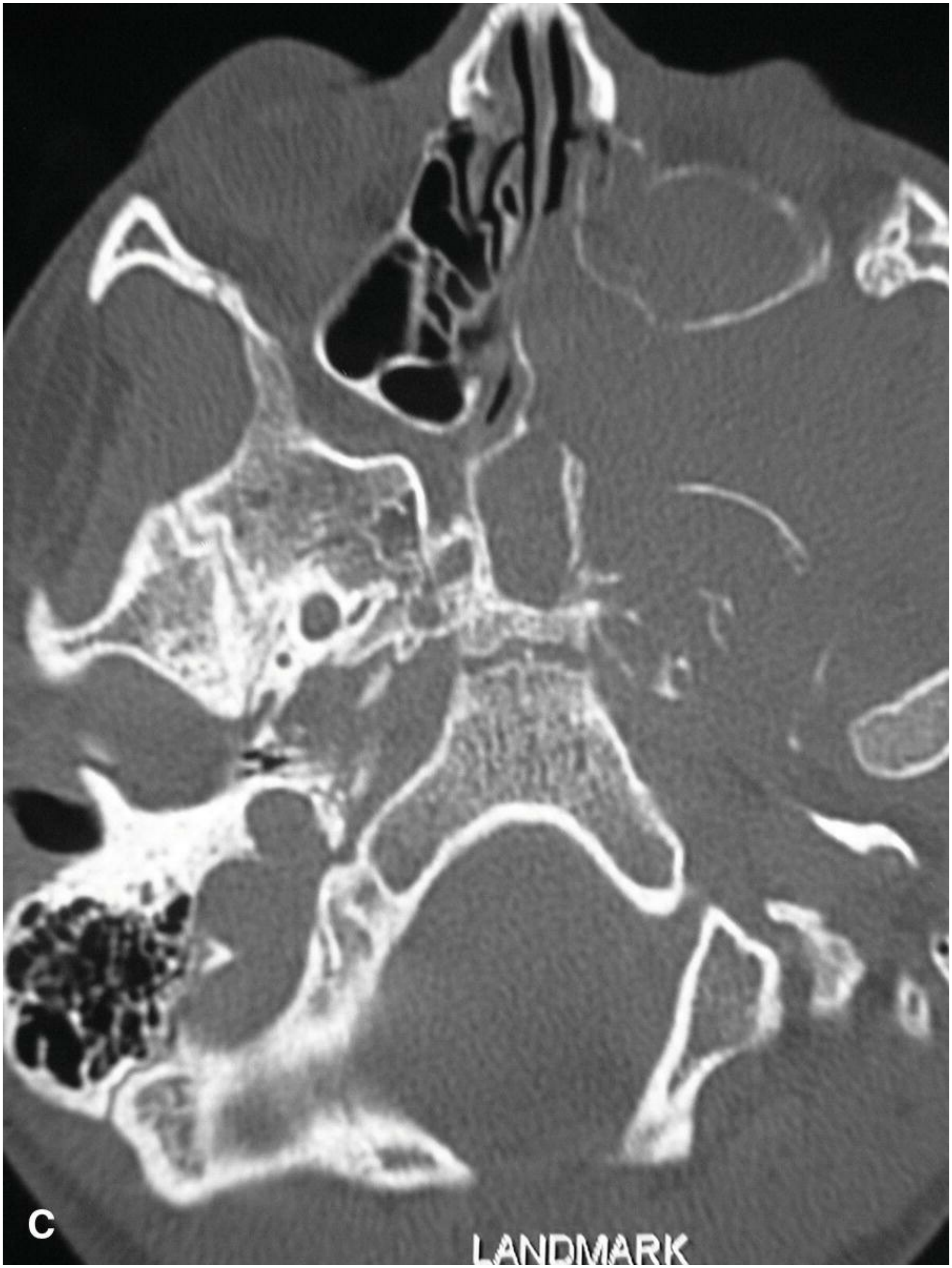
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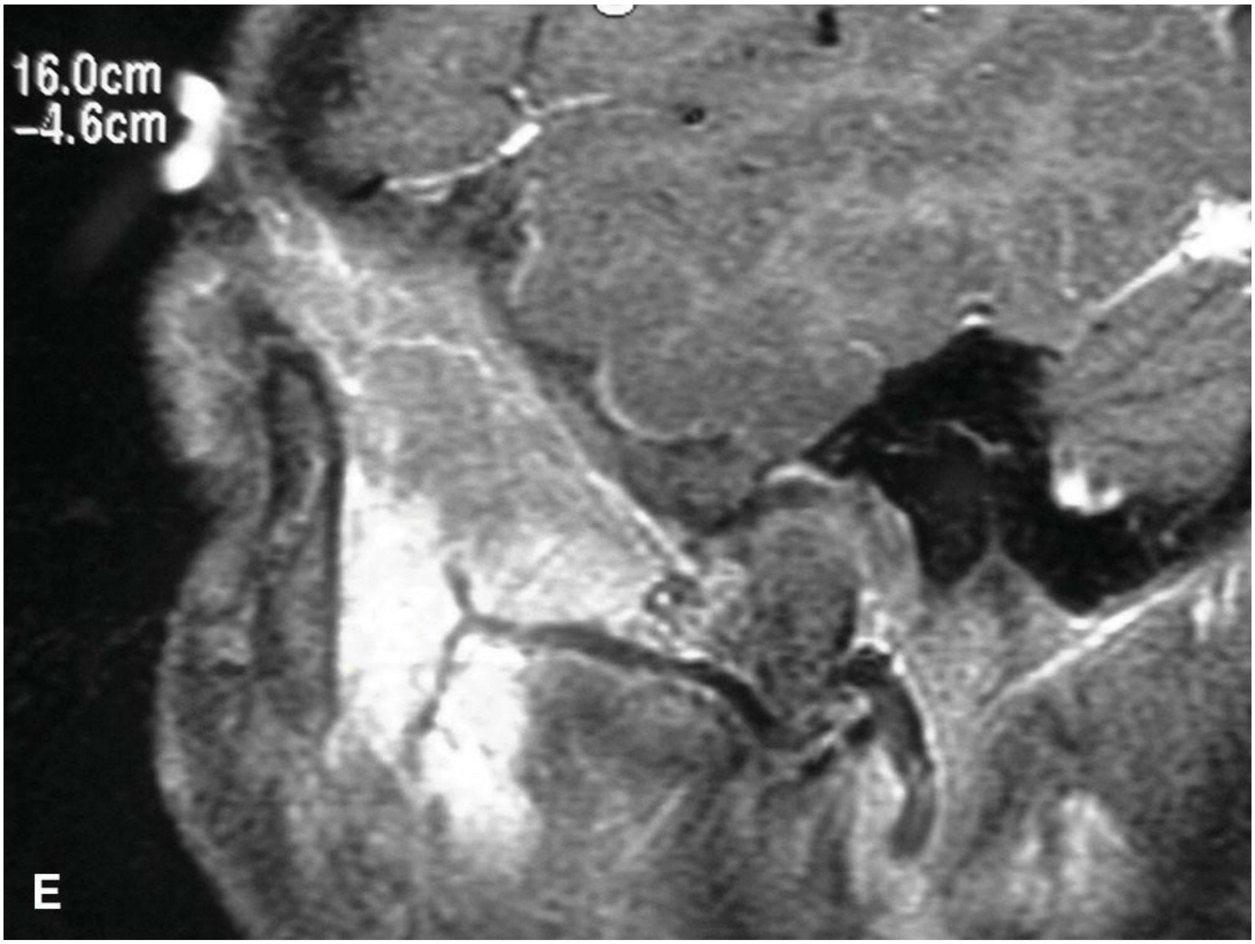
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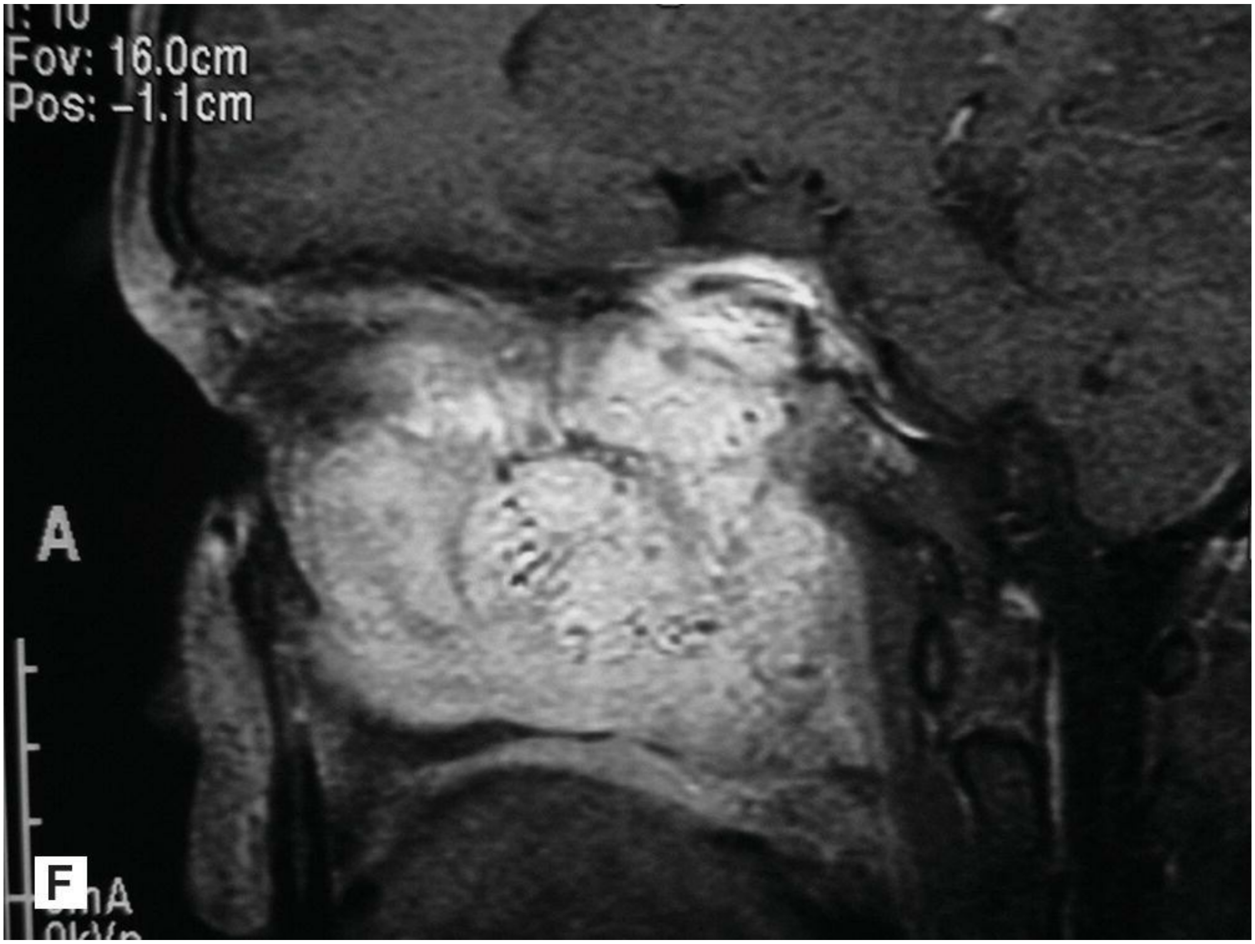
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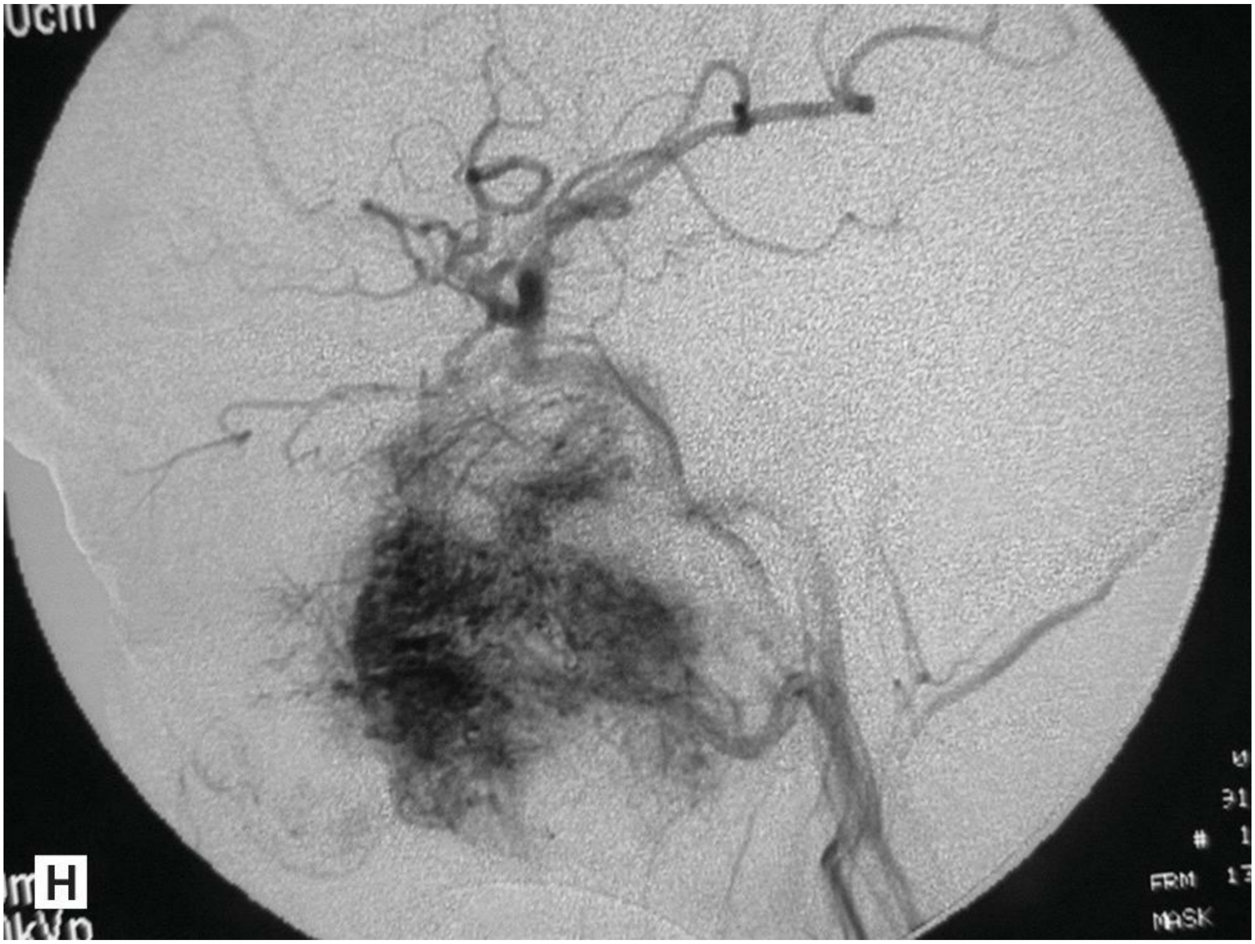

Figure 10.20. Juvenile nasopharyngeal angiofibroma. Coronal **(A, B)** and axial **(C)** CT with contrast and axial T1 axial MRI with contrast (**D**) showing the mass in the nasal cavity, maxillary sinus, nasopharynx, sphenoid sinus, pterygoid plates, and pterygopalatine and infratemporal fossa. The mass involves the floor of the middle cranial fossa and extends intracranially to the cavernous sinus. T1 sagittal MRI **(E, F)** show flow voids of increased extensive vascular supply coming from the internal maxillary artery **(E)** and internal carotid artery **(F)**. Early-phase angiogram showing the blood supply from the internal maxillary artery **(G)** and late phase showing significant tumor vascular blush and contribution from the internal carotid artery **(H)**.

Biopsy

The definitive diagnosis of a neoplasm of the nasal cavity and paranasal sinuses relies on expert histopathologic review of any biopsy specimens by a head and neck pathologist to confirm the exact diagnosis prior to treatment. This is critical because the treatment and prognosis of sinonasal cancer is

greatly influenced by histology.[41,42] This is particularly true for neuroendocrine tumors in which the misdiagnosis rate is particularly high. In a study from MDACC, patients referred with a presumed diagnosis of ENB were frequently reclassified to other types of tumors including NEC, sinonasal undifferentiated carcinoma (SNUC), melanoma, and even pituitary adenoma.[43] The implications of this misdiagnosis are far reaching and required significant alteration in the initially proposed treatment plan in a significant number of patients.

Biopsy of Tumors of the Nasal Cavity

The vast majority of sinonasal neoplasms are accessible for biopsy through a strictly endonasal approach. A wide variety of rigid nasal endoscopes offer superb visualization of intranasal lesions with a high degree of optical resolution and bright illumination (Fig. 10.13). The application of topical anesthetics and decongestants improves visualization and allows thorough examination of the nasal cavity. The site of origin of the lesion and its relation to the nasal walls (septum, floor, roof, and lateral nasal wall) should be noted. An adequate specimen should be obtained, avoiding crushing of tissue, and submitted for histopathologic examination. If the diagnosis of lymphoma is suspected, fresh tissue should be sent in saline, rather than fixed in formalin. Most endonasal biopsies can be performed in the outpatient setting with minimal discomfort to the patient. In certain cases, the diagnosis of a highly vascular neoplasm, such as angiofibroma, may be suspected on clinical grounds. Under these circumstances, it is prudent not to perform the biopsy until imaging and angiography (possibly with embolization) are performed (Fig. 10.20). Preoperative biopsy can then be performed in the operating room under controlled conditions to confirm the diagnosis before surgical resection. If a nasal mass is suspected to have an intracranial communication such as an encephalocele, meningocele, or nasal glioma, this should be confirmed with imaging to avoid inadvertent CSF leak and subsequent meningitis (**Fig. 10.21**).

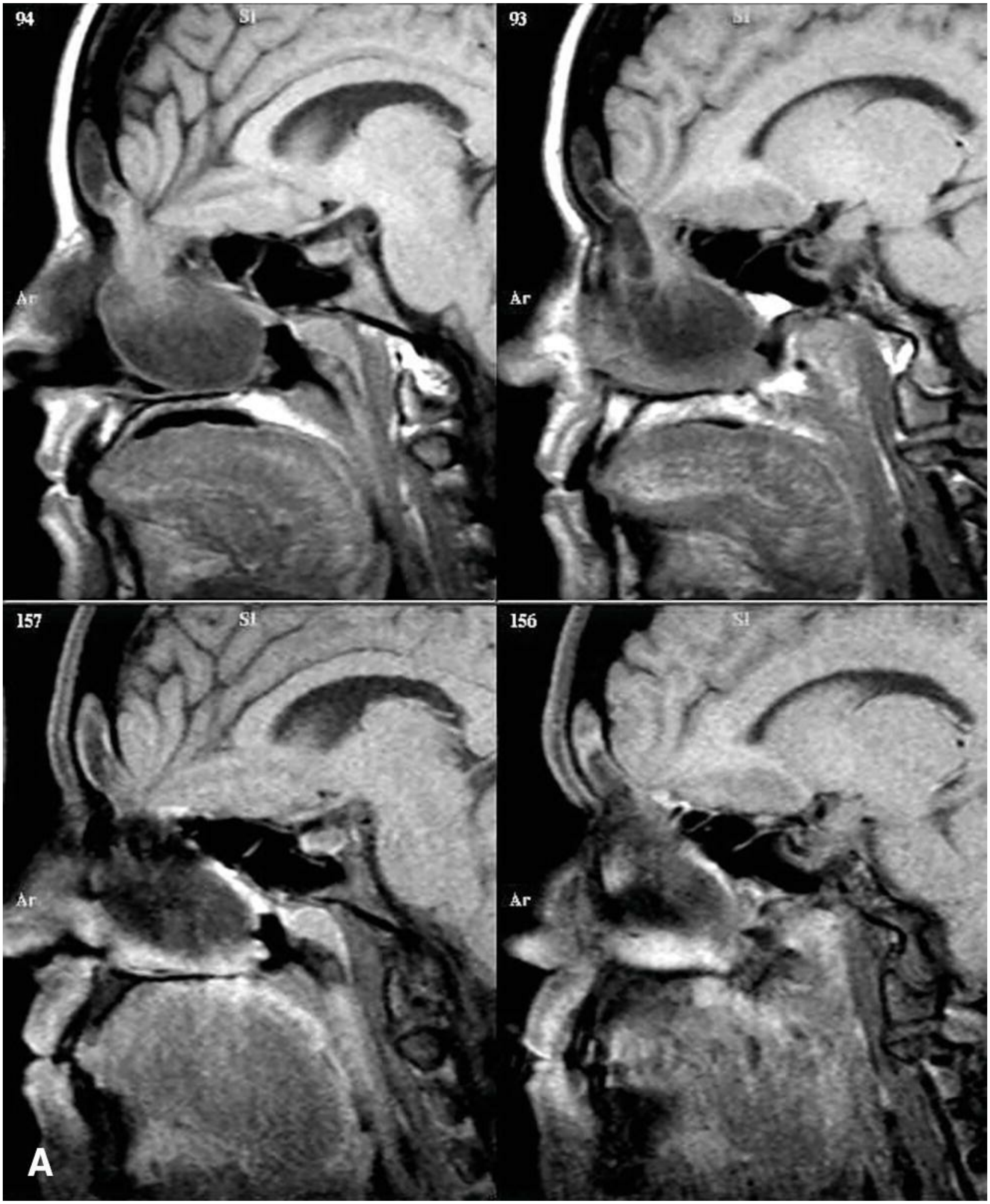
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Figure 10.21. Meningoencephalocele. Sagittal **(A)** and coronal **(B)** T1 MRI with gadolinium showing a defect in the anterior cranial base at the right fovea ethmoidalis and cribriform plate. There is herniation of a meningoencephalocele, which presented as a nasal mass. Inadvertent biopsy

of such lesions may lead to CSF leaks and should be avoided.

Biopsy of Tumors of the Paranasal Sinuses

In the unusual case where a paranasal sinus neoplasm is confined to the sinus cavity and does not present itself intranasally, a biopsy should be obtained by direct access to the involved sinus. Tumors of the maxillary sinus can still be accessed through an endoscopic approach by creating a wide antrostomy in the region of the natural ostium. Otherwise, the maxillary sinus is accessible through a sublabial incision in the canine fossa via an anterior antrostomy. The ethmoidal sinus can be approached endonasally through endoscopic ethmoidectomy. Alternatively, an external ethmoidectomy approach provides a direct access via a Lynch incision.

The sphenoid sinus is easily approached endoscopically in the vast majority of cases. The use of C-arm fluoroscopy or more recently computer-assisted three-dimensional (3-D) intraoperative imaging is sometimes used in cases with difficult access or unusual anatomy. Isolated tumors of the frontal sinus are rare. A trephination through the floor of the sinus is utilized for biopsy of lesions within its cavity.

TREATMENT

Surgical Treatment

Indications

Surgical resection, alone or more commonly combined with adjunctive therapy, remains the mainstay of treatment of cancers of the SNT. This approach seems to provide the best chances for cure or control of disease. For early-stage disease (T1 to T2), surgery alone may be adequate treatment, but for more advanced stage resectable disease, postoperative adjuvant radiation or chemoradiation is commonly used to improve tumor control. Surgery is indicated whenever there is adequate evidence that the tumor can be completely resected with acceptable morbidity. The development of new combined craniofacial approaches has extended the indications of surgery to include some patients with skull base and even intracranial extension.[44,45]

The advent of new reconstructive techniques, including microvascular free flaps, pericranial flaps, and prosthetic rehabilitation, has reduced morbidity and improved rehabilitation following extensive resections of advanced sinonasal cancer.[46–48] In the presence of tumor extension to the CS, internal carotid artery, optic chiasm, extensive brain parenchymal involvement, or distant metastasis, surgery is usually contraindicated. However, in selected cases, surgery with proper adjuvant therapy may still offer the most effective local disease palliation even in the presence of extensive disease.

Preoperative Preparation

A thorough preoperative assessment should determine the candidacy of a patient for surgical management of his or her neoplasm. This involves a careful “mapping” of the tumor extent, as well as the general medical condition and functional status of the patient. This is usually accomplished by a detailed history and physical examination and comprehensive examination of the head and neck region including endoscopy of the sinonasal region. Cranial nerve examination as well as ophthalmologic evaluation should be done to evaluate cranial base and orbital extension, respectively. High-resolution imaging should be obtained using CT or MRI, or both, to accurately assess the tumor extent. In certain cases, angiography will be needed to determine the extent of carotid arterial involvement. The balloon occlusion test should be performed if carotid artery resection or reconstruction is contemplated. Preoperative embolization may be indicated in certain vascular tumors.

Neurosurgical consultation is needed if a combined craniofacial approach is anticipated. If free vascularized flaps will be utilized for reconstruction, expertise with microvascular surgery is needed, and appropriate consultation should be obtained. Evaluation by a maxillofacial prosthodontist is required in most patients to obtain preoperative dental impressions and design surgical obturators or splints for maintenance of proper dental occlusion and oral rehabilitation. Similar expertise is essential in cases where prosthetic orbital, nasal, or facial rehabilitation is required. Consultations with medical and radiation oncology colleagues should be done to consider incorporation of chemotherapy or radiation in the treatment plan. Radiation and/or chemotherapy may be used preoperatively as induction (neoadjuvant) or postoperatively as adjuvant therapy. This is particularly important in patients

with advanced stage disease (e.g., dural or orbital involvement) or high-grade lesions (e.g., SNUC). In selected cases, chemotherapy and/or radiation may be reasonable alternatives to surgery. Such decisions are best discussed in the format of a multidisciplinary tumor board. If surgery is chosen as a treatment modality, the plan for the surgical approach, the extent of resection, and reconstructive options should then be formulated. This plan should be communicated clearly among the various members of the surgical team particularly the otolaryngologists, head and neck surgeons, neurosurgeons, and plastic and reconstructive surgeons.

Careful assessment of the patient’s general medical condition should be carried out prior to surgery. Preoperative chest radiograph, blood counts, liver and renal function tests, blood sugar, electrolytes, coagulation studies, and an electrocardiogram (ECG) should be performed routinely. Appropriate consultations from medical colleagues should be obtained in order to optimize the patient’s medical status before surgery and help in management postoperatively. The patient’s nutritional status should be evaluated, and if indicated, enteral or parenteral feeding may be considered. High-resolution imaging for metastatic workup is not routinely performed, unless indicated by history, clinical examination, chest radiograph results, or blood test abnormalities.

Finally, the surgical team should discuss with the patient and family the nature of the disease, the evaluation, and the indications, risks, possible complications, sequelae, and alternatives of therapy. The expected postoperative course including length of stay in the hospital, feeding, rehabilitation, and need for adjunctive therapy should be described. This ongoing communication should be maintained in a clear, honest, and sympathetic fashion throughout the course of patient care.

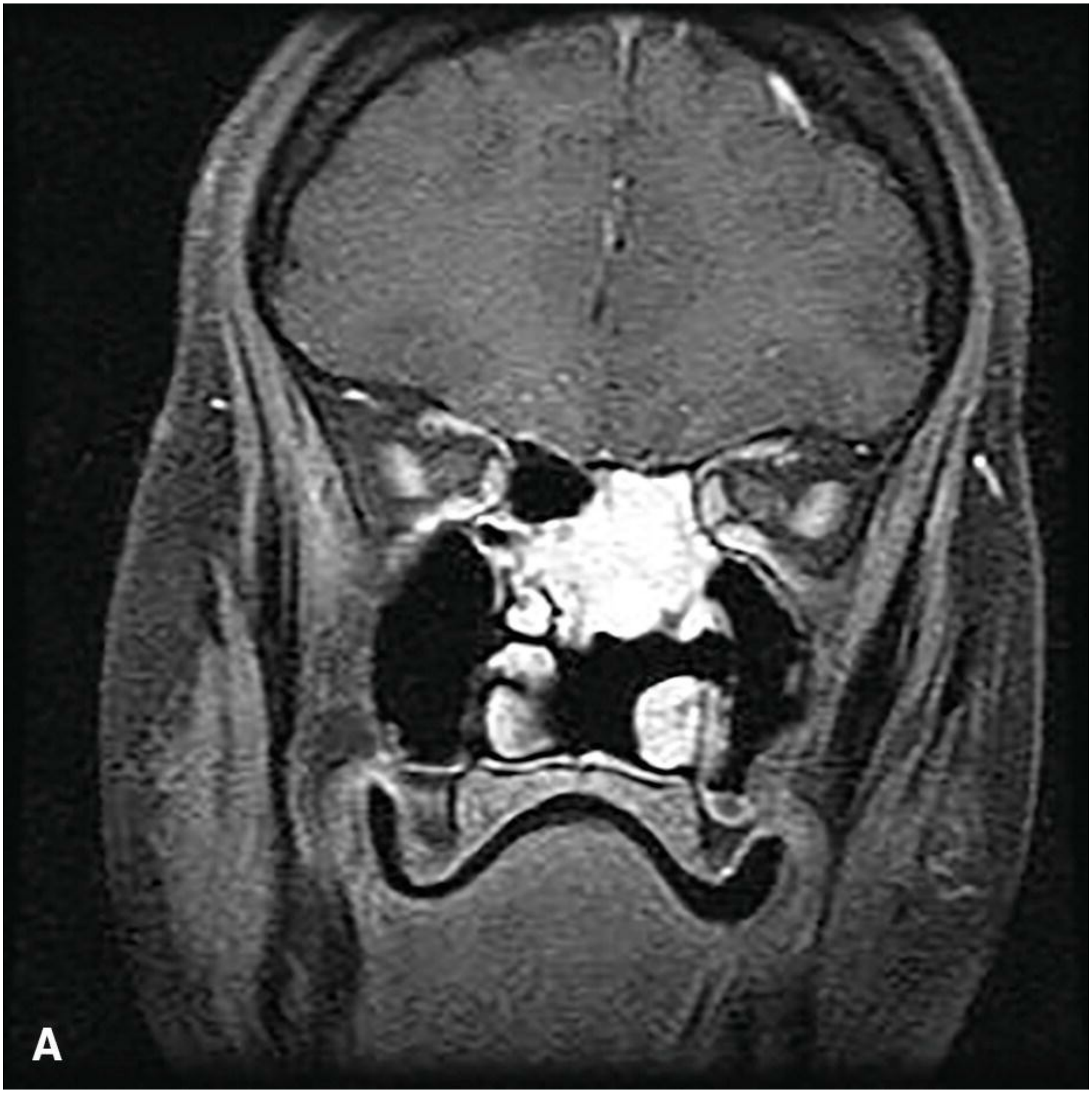
Surgical Principles

When dealing with the subject of surgical treatment of sinonasal cancer, a distinction has to be made between the terminology used to describe the surgical approach on the one hand and the extent of resection on the other hand. A surgical approach describes the various incisions, soft tissue dissection, and skeletal osteotomies required to expose the tumor and adjacent structures to perform a complete and safe resection. On the other hand, the extent of tumor resection describes the various structures that need

to be surgically extirpated to achieve total tumor removal with tumor-free margins. Obviously, both the surgical approach and the extent of resection are closely related and depend on the extent of tumor, its aggressiveness, and related critical structures. The various surgical approaches and extent of resection are listed in **Table 10.3**.[44] The choice of surgical approach and extent of resection will generally depend on the location and the extent of the tumor. In some cases, different approaches may be equally effective for resection of a particular tumor. For example, a tumor of the nasal cavity, lateral nasal wall, ethmoid, sphenoid, and medial maxillary sinus requiring a medial maxillectomy and a total sphenoethmoidectomy may be adequately resected using a transfacial, endoscopic, or sublabial approach (Figs. 10.18 and **10.22**). However, the following principles should always guide the surgeon in choosing the optimal approach and extent of resection for all patients undergoing surgical treatment of sinonasal cancer:

Table 10.3 Surgical Approaches and Extent of Resection of Cancers of the Sinonasal Tract

Surgical Approach
Endoscopic
Lateral rhinotomy and Weber-Fergusson
Transoral–transpalatal
Facial “degloving”
Craniofacial
Extent of Resection
Ethmoidectomy
Inferior maxillectomy
Medial maxillectomy
Total maxillectomy
Anterior cranial base resection
Infratemporal fossa dissection
Orbital exenteration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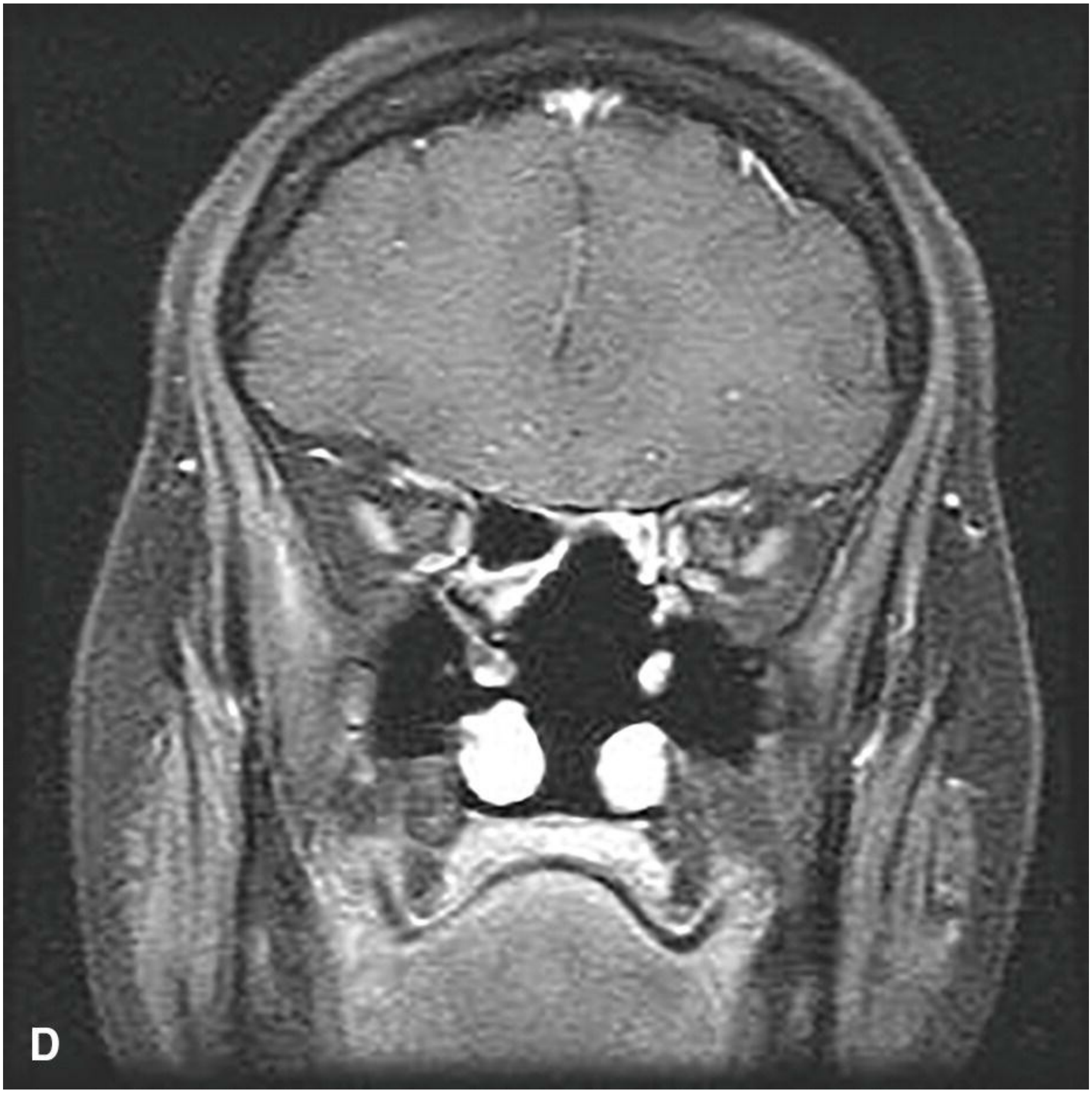

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E

Figure 10.22. Hemangiopericytoma of the sinonasal region. Preoperative **(A–C)** and 3 years postoperative **(D–F)** MRI of a patient who underwent endoscopic resection of hemangiopericytoma of the sinonasal tract.

- Adequate oncologic resection
- Minimal brain retraction
- Protection of critical neurovascular structures
- Meticulous reconstruction of the skull base
- Optimal esthetic outcome

Surgical Approaches

Endonasal.

Endoscopic endonasal approaches (EEAs) are being increasingly used for surgical excision of selected tumors of the SNT, either alone or in combination with open approaches. Endoscopic surgery avoids craniofacial soft tissue dissection, skeletal disassembly, and brain retraction. Other advantages of EEA include direct bilateral access to the tumor, superior illumination, magnification and visualization of the surgical field (Fig. 10.7), wider angles of vision using angled endoscopes, and relatively less morbidity compared to the open surgical approaches.

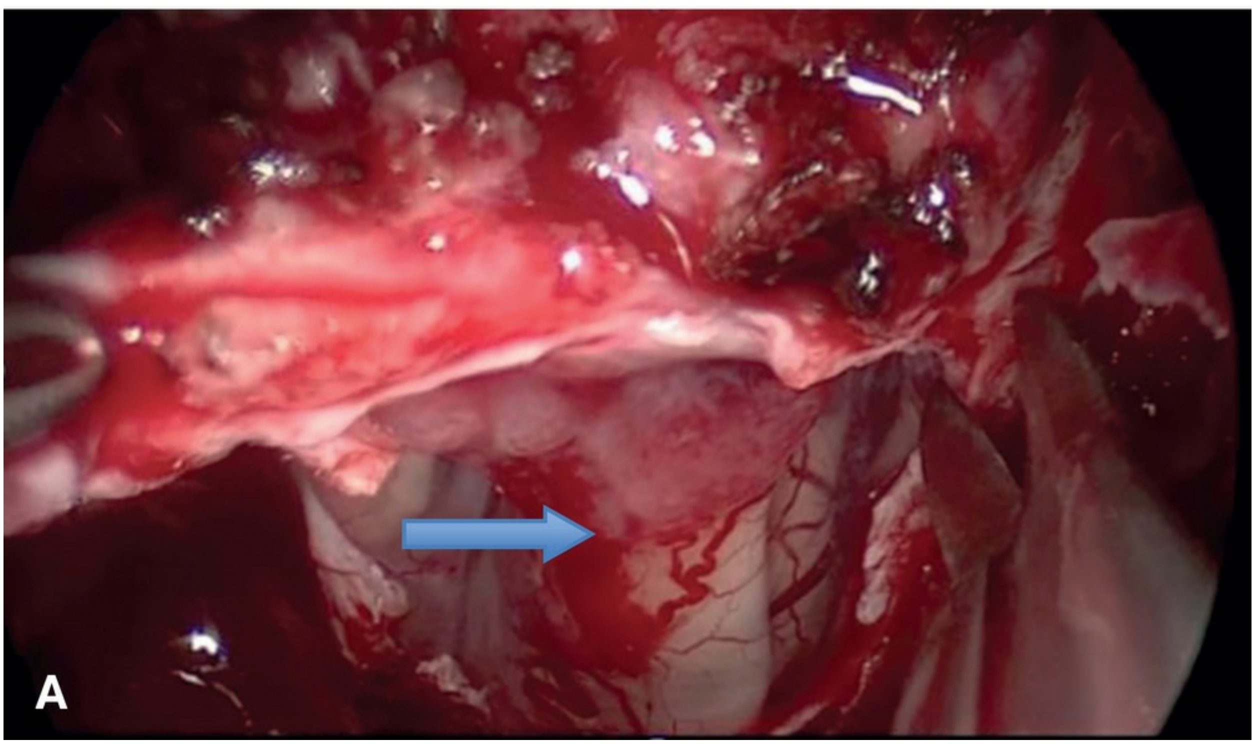
When endoscopic endonasal surgery was first advocated for the treatment of sinonasal malignancies, concerns were raised regarding the oncologic soundness of the procedure.[49] Criticisms have centered on the inability of the endoscopic approach to perform an en bloc resection. Proponents of the endoscopic technique argue that unless the tumor is small, en bloc resection is rarely achievable with open surgery.[50,51] Several studies have shown that the method of resection (en bloc vs. piecemeal) does not significantly impact on oncologic outcomes and that what is paramount, however, is achieving negative resection margins, regardless of the surgical approach.[52,53]

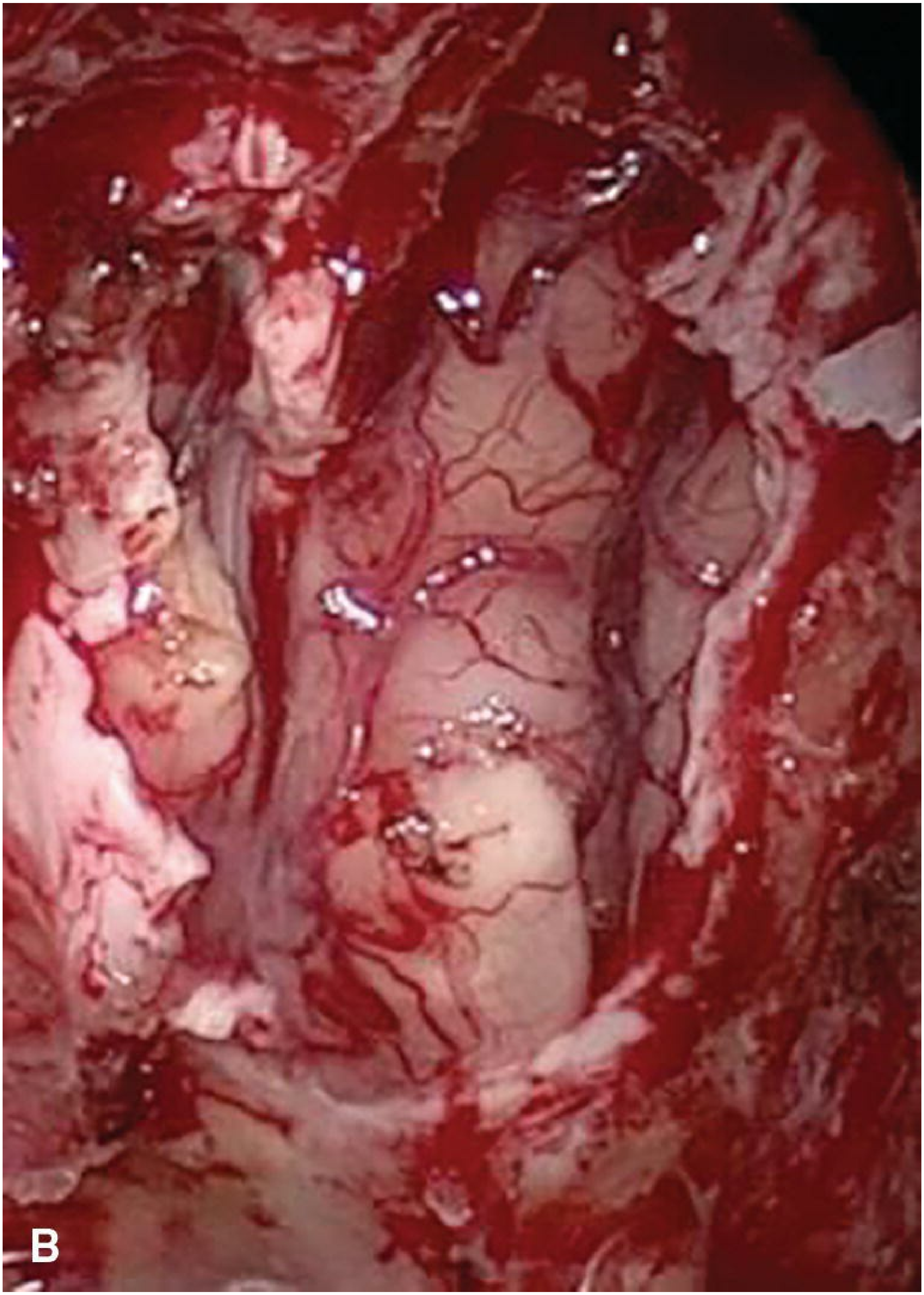
Over the past decade, there has been increasing evidence regarding the safety and oncologic effectiveness of these techniques. Several institutions have reported their experience with endoscopic surgery and have shown reduced morbidity, shorter hospital stay, better quality of life, and equivalent survival outcomes to those of open surgery in carefully selected patients.[54]

The keys to adequate oncologic results using EEA are good selection of patients and the surgeon’s experience with this approach. EEA are most suited for central tumors involving the nasal septum, nasal cavity and lateral nasal wall, ethmoid and sphenoid sinuses, and clivus (Fig. 10.22). Tumors with extension into the facial soft tissue, involvement of the anterior wall of the frontal sinus, deep orbital invasion, lateral supraorbital extension, or significant brain parenchymal invasion are not readily accessible with EEA and require the addition of an open approach.

The surgical technique of EEA to the sinonasal region and the anterior skull base has been previously described in detail.[51] The standard endoscopic

endonasal “craniofacial” resection starts with debulking of the intranasal tumor, identifying the attachment of tumor origin and resection of the sinonasal component. A posterior septectomy provides a binasal approach for the surgeon and the assistant allowing a four-hand technique for dissection. If not involved by tumor, a vascularized nasal septal flap is developed contralaterally based on the posterior septal branch of the sphenopalatine artery. In some cases, when the tumor does not involve the septum, this flap can be developed ipsilaterally or bilaterally. A complete anterior and posterior ethmoidectomy are then performed, and the sphenoid sinuses are opened bilaterally. The bony skull base is skeletonized from the frontal sinus anteriorly to the planum sphenoidale posteriorly, bilaterally. The medial orbital walls are also skeletonized bilaterally, delineating the lateral extent of the surgical corridor. After control of vascular supply from the anterior and posterior ethmoid arteries, the lamina papyracea, fovea ethmoidalis, cribriform plate, crista galli, and planum sphenoidale can be removed with high-speed diamond drill with copious irrigation to avoid heat injury to critical neural structures. After removing the bone of the anterior central skull base, the dura, olfactory bulbs and tracts, and periorbita can be resected depending on the extent of tumor involvement (**Fig. 10.23**).

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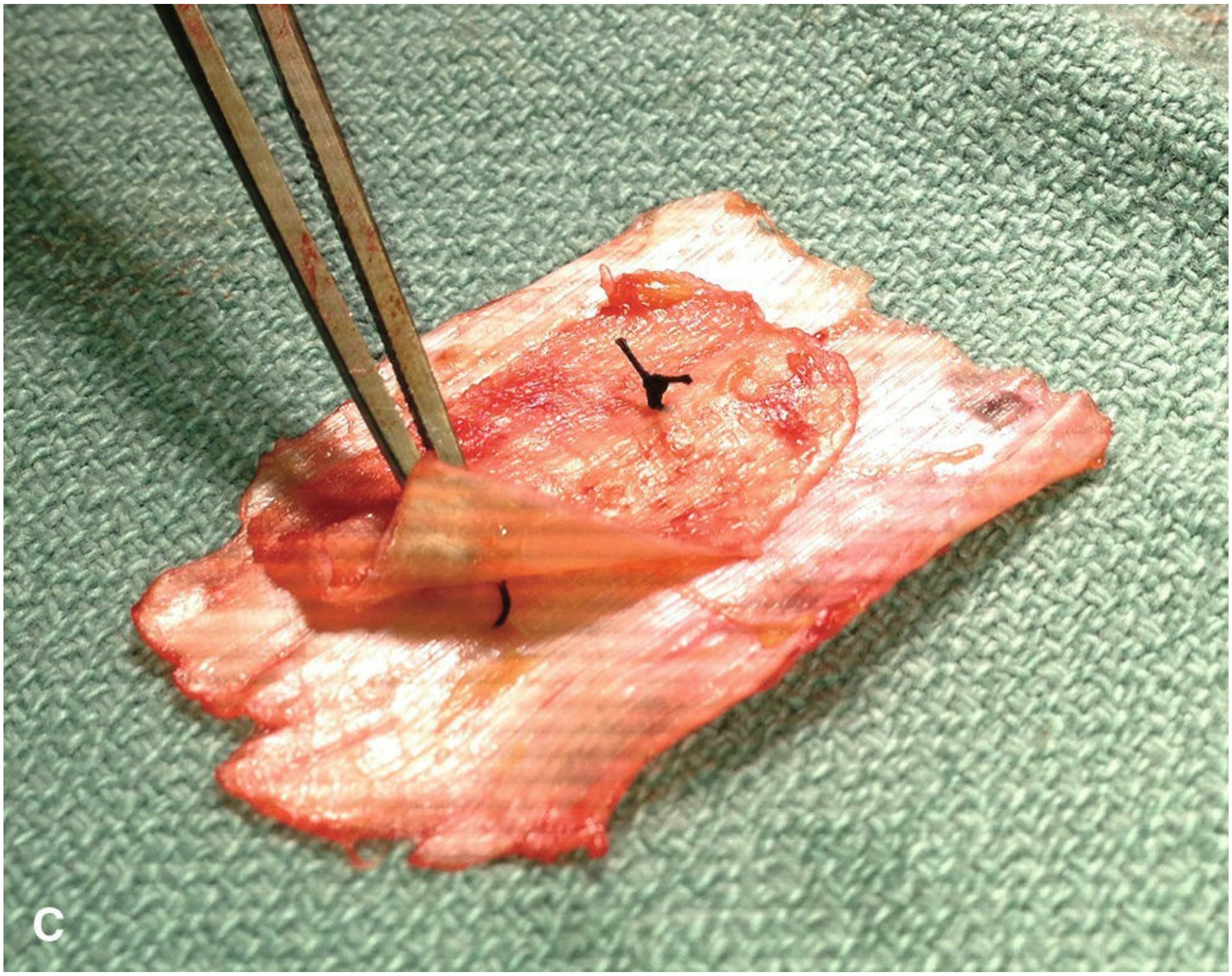
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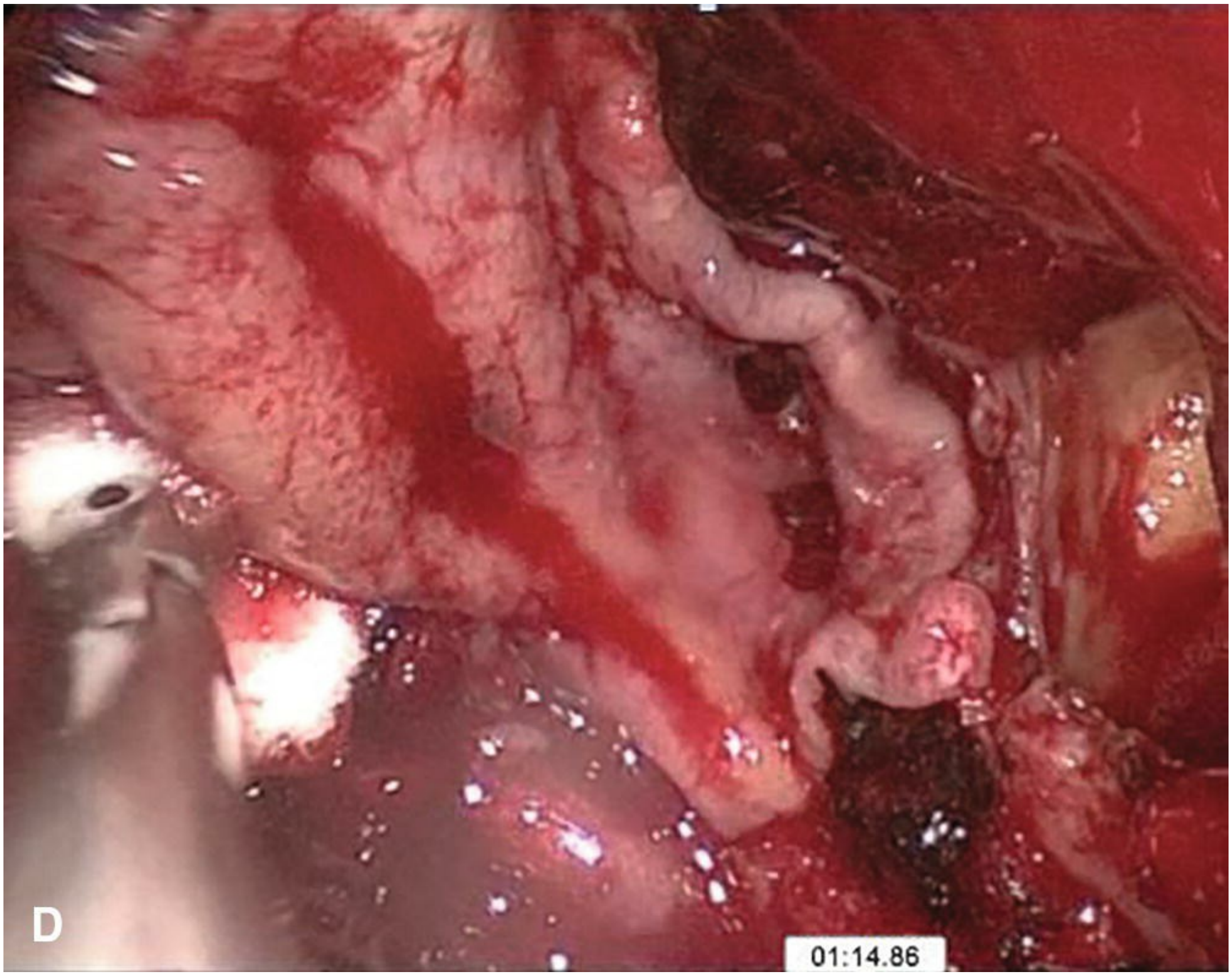


Figure 10.23. A: Intraoperative endoscopic view of a patient with ENB. The dura is opened, and the tumor is seen to arise from the olfactory bulb. **B:** Tumor resection is complete, and the dural defect is shown. **C:** Fascia lata graft is harvested. A double layer is created with the smaller one to be placed intradurally and the larger is placed extradurally but underneath the bony defect of the skull base (intracranially). Both layers are sutured together to stabilize them during placement and obliterate any dead space between them. **D:** A vascularized nasoseptal flap based on the posterior septal branch of the sphenopalatine artery is rotated to cover the double layer graft.

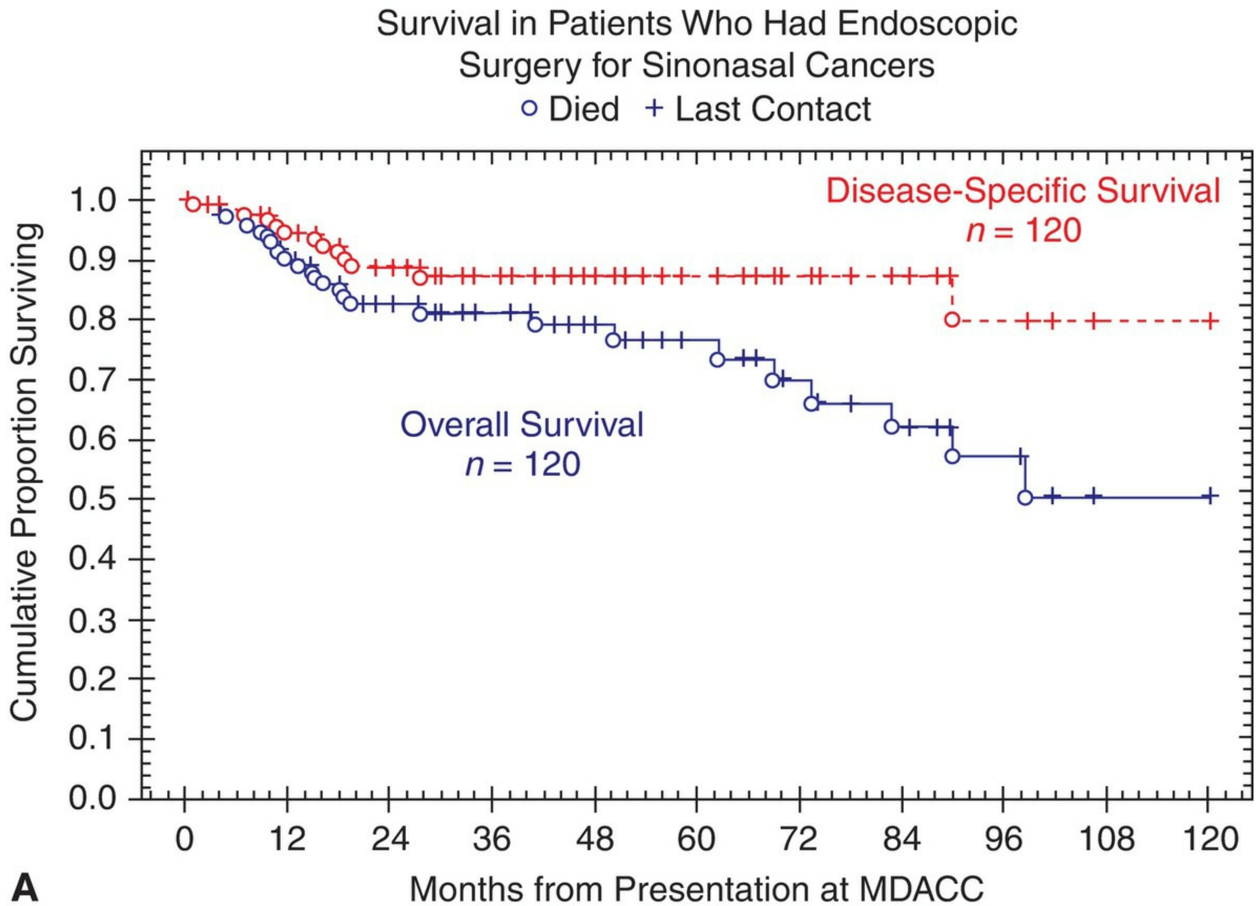
Reconstruction of the skull base in the early stages of development of EEA was a major challenge, but has significantly evolved over the last decade. Early reconstructive experience was associated with CSF leak rates of 20% to 30% for EEA of the anterior skull base.[55,56] The application of a nasoseptal flap placed extradurally has lowered leak rates to 5% (Fig.

10.23).[57] When there is tumor involvement of the superior nasal septum, the "extended nasoseptal flap" can be harvested from the lower septum and extended onto the floor and lateral wall of the nasal cavity.[58] Other vascularized reconstructive alternatives for the anterior skull base include minimally invasive pericranial flap,[59] the middle turbinate flap for small defects and the transpterygoid temporoparietal fascia flap.[60,61] The inferior turbinate flap, while robust, has limited reach and is best suited to clival defects.[62] Other flaps described in the literature such as the palatal flap,[63] the buccinator myomucosal flap,[64] and the occipital galeopericranial flap [65] may be considered.

Some investigators have utilized nonvascularized reconstructive options with favorable results. Gil et al.[66] described a double-layered tensor fascia lata repair with a CSF leak rate of 0.8%. Histologic examination of resected fascia lata in patients who received a second operation shows evidence of neovascularization of the fibrous tissue, even without the presence of a vascularized flap. Villaret et al.[67] proposed a three-layer reconstruction with the iliotibial tract. They report postoperative CSF leak rates of around 4%. In cases where the skull base and dural defect are too large for purely endoscopic reconstruction, an open approach may provide the safest way to achieve reliable cranionasal separation and avoid CSF leak and the risk of meningitis.[68,69]

The long-term oncologic results of EEA in treating malignant sinonasal tumors are still being defined. The two largest series from North America[69] and Europe[68] have demonstrated endoscopic resection to have comparable oncologic results to open surgery. Hanna et al.[69] reported on 120 patients treated at MDACC from 1992 to 2007. An endoscopic endonasal approach was used in 77% of patients, and the cranioendoscopic approach (CEA—defined as transnasal endoscopic approach with the addition of a frontal or subfrontal craniotomy) was used in 23% of patients. Approximately two-thirds of patients in the EEA group had T1 to T2 tumor stage, whereas 95% of patients in the CEA group had T3 to T4 disease stage ($p < 0.01$). Positive margins were reported in 15%. Postoperative radiation therapy or chemoradiotherapy was used in 50% of patients. With a mean follow-up of 37 months, the local, regional, and distant recurrence was 15%, 6%, and 5%, respectively. The 5- and 10-year disease-specific survival (DSS) were 87%

and 80%, respectively (**Fig.** 10.24**A**). Disease recurrence and survival did not significantly differ between the EEA and CEA group (**Fig. 10.24B**). The authors emphasized the role of appropriate adjuvant therapy and treatment by expert multidisciplinary teams in the management of sinonasal malignancies. Nicolai et al.[68] reported on 184 patients from the University of Brescia and the University of Pavia/Insubria-Varese, treated from 1996 to 2006. The overall 5-year DSS was 82%. At the mean follow-up of 34 months, the local, regional, and distant recurrence was 15%, 1%, and 7% of patients, respectively. Both study cohorts had similar distributions of T staging, adjuvant treatment, and the proportion of EEA to CEA (**Table 10.4**). However, compared to the MDACC group, patients in the European group were older, were predominantly male, were less likely to have had prior treatment (28% vs. 58%), and were more likely to present with adenocarcinoma (37% vs. 14%). Irrespective of these differences, the 5-year DSS for the two series is comparable to those reported in the open anterior cranio-facial resection (ACFR) cohorts. Both groups concluded that in well-selected patients, endoscopic resection of sinonasal cancers results in acceptable oncologic outcomes.



Survival in Patients Who Had Endoscopic
Surgery for Sinonasal Cancers
○ Died + Last Contact
Disease-Specific Survival
n = 120
Overall Survival
n = 120
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
72
84
96
108
120
Months from Presentation at MDACC

A

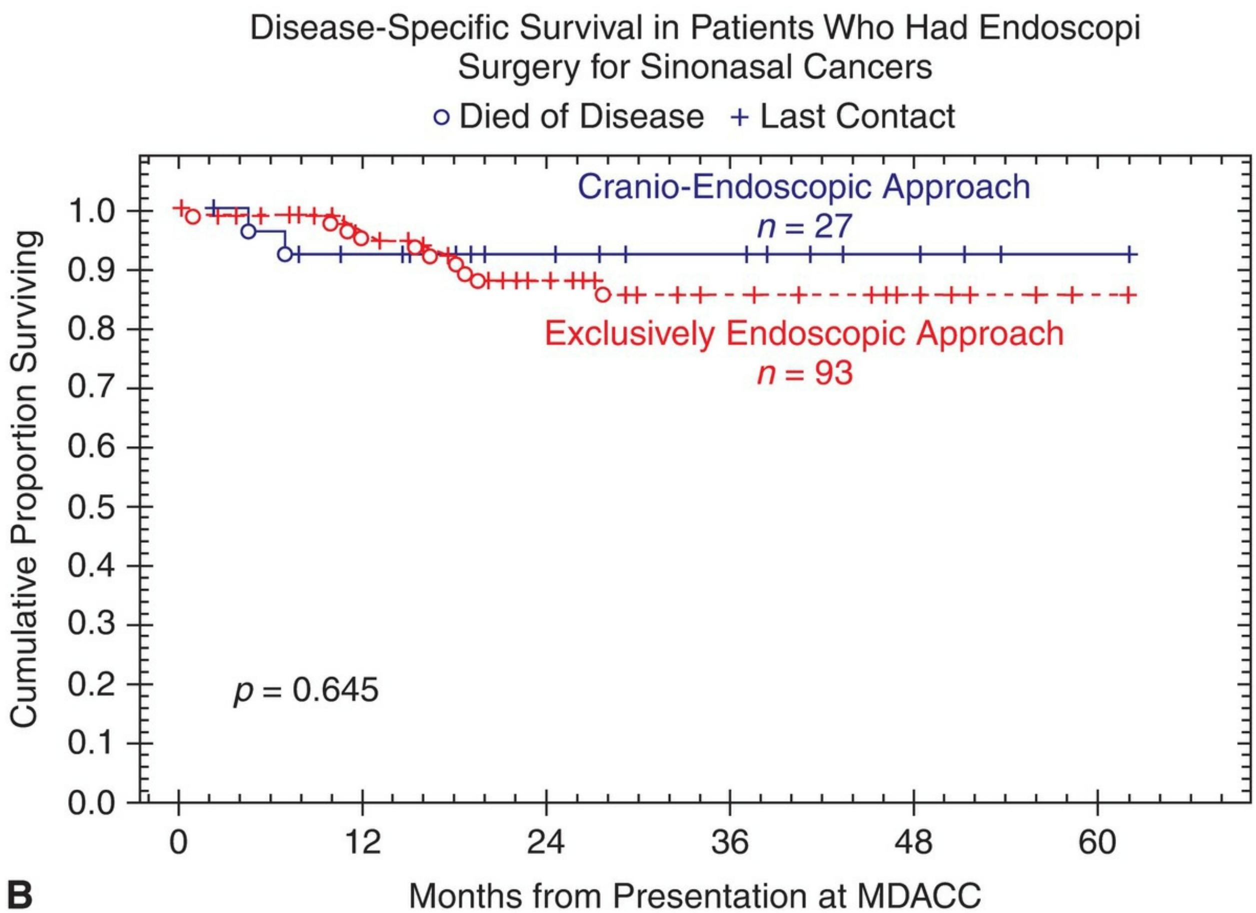


Figure 10.24. A and B: Survival in patients who underwent endoscopic resection of sinonasal cancers at MDACC. (Hanna E, et al. Endoscopic resection of sinonasal cancers with and without craniotomy: oncologic results. Arch Otolaryngol Head Neck Surg. 2009;135(12):1219–1224, Ref. 69.)

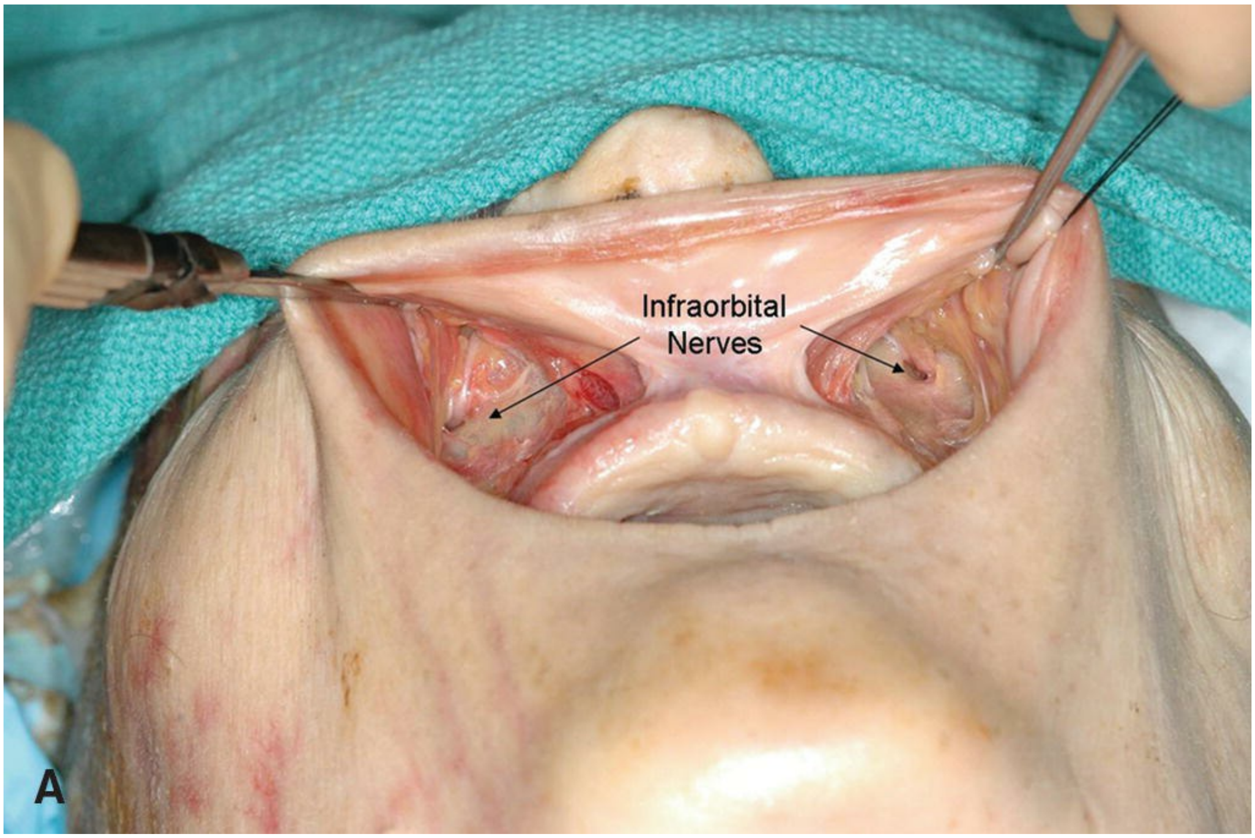
Table 10.4 Comparison of Results from Two Large Studies of Oncologic Outcomes of Endoscopic Resection of Sinonasal Malignancy

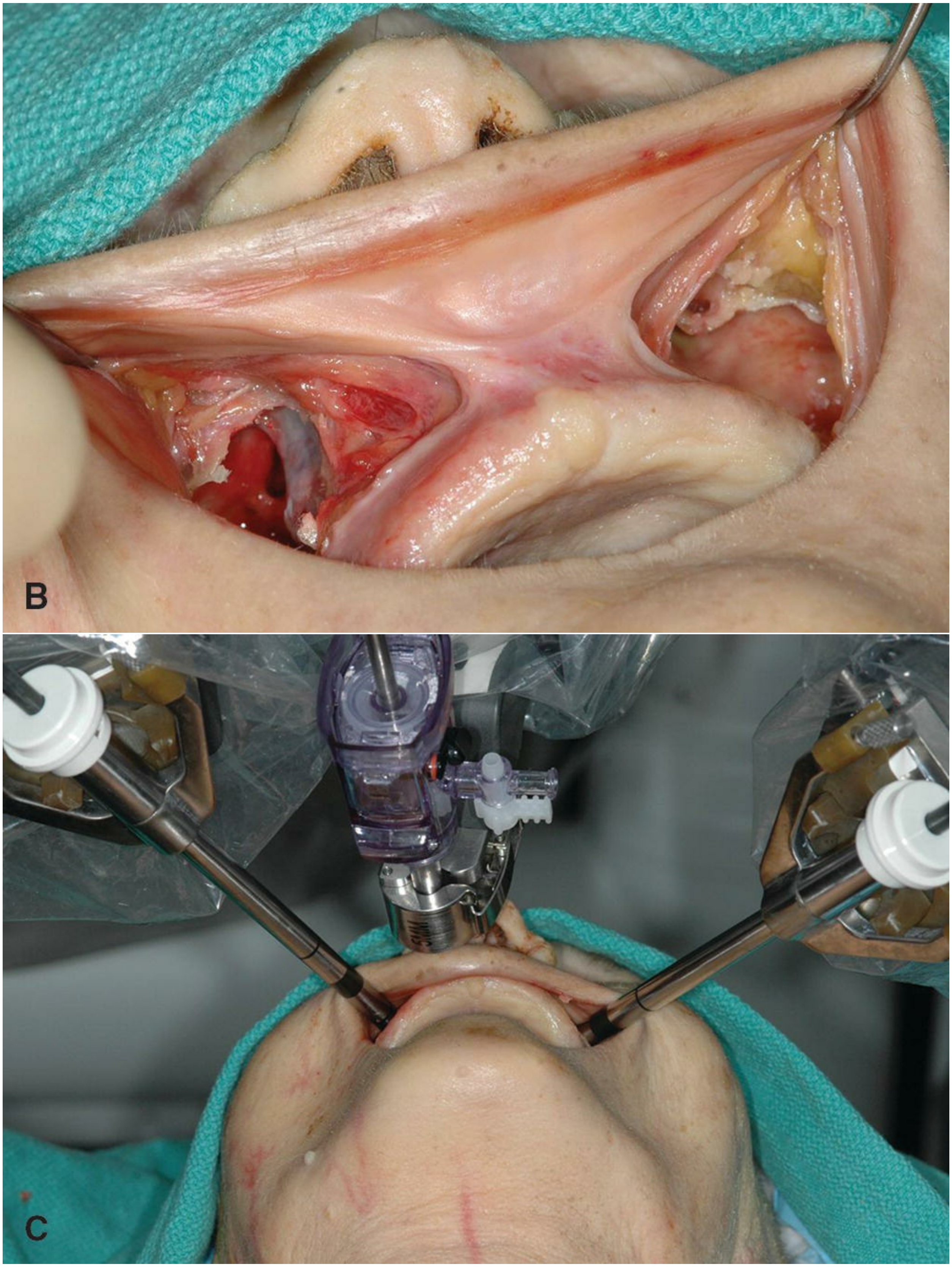
Findings	Hanna et al.[69]: MD Anderson Cancer Center			Nicolai et al.[68]: U. Brescia and U. Pavia/Insubria-Varese		
Number of patients						
Total	120			184		
EEA	93 (77.5%)			134 (73%)		
CEA	27 (22.5%)			50 (27%)		
Mean follow-up	37 mo			34 mo		
Prior treatment	59%			28%		
Stage	EEA	CEA	All patients	EEA	CEA	All patients
T1	32%	0%	25%	37%	6%	28%
T2	31%	5%	25%	19%	2%	14%
T3	17%	36%	21%	15%	24%	17%
T4	20%	59%	29%	16%	62%	28%
Histopathology						
Adenocarcinoma	14%			37%		
Esthesioneuroblastoma	17%			12%		
Melanoma	14%			9%		
Squamous cell carcinoma	13%			14%		
Adenoid cystic carcinoma	7%			7%		
Neuroendocrine carcinoma	4%			1%		
SNUC	2%			3%		
Sarcomas	15%			13%		
Findings	Hanna et al.[69]: MD Anderson			Nicolai et al.[68]: Italy		
Adjuvant therapy						
None (surgery only)	50%			47%		
Radiation	37%			39%		
Chemoradiation	13%			3%		
Chemotherapy	6%			4%		
Recurrence						
Local	15%			15%		
Regional	6%			1%		
Distant	5%			7%		
5-year disease-specific survival						
Overall	87%			82%		
EEA	86%			91%		
CEA	92%			59%		

From Hanna E, et al. Endoscopic resection of sinonasal cancers with and without craniotomy: oncologic results. *Arch Otolaryngol Head Neck Surg.* 2009;135(12):1219–1224; Nicolai P, et al. Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: a 10-year experience. *Am J Rhinol.* 2008;22(3):308–316.

The limitations of EEA include lack of binocular vision and depth perception, which is important when dealing with critical neurovascular structures. Ergonomic limitations include the inability of the primary surgeon to control the endoscope and two instruments simultaneously and hence the reliance on

a surgical assistant for camera control during two-handed surgery. The major limitation of EEA is the inability to repair or patch dural defects with suture techniques, which limits the reconstructive options after endoscopic resection of intradural tumors. We continue to explore novel applications in robotic endoscopic skull base surgery to overcome some of these limitations[70]–[73] (**Fig. 10.25**).

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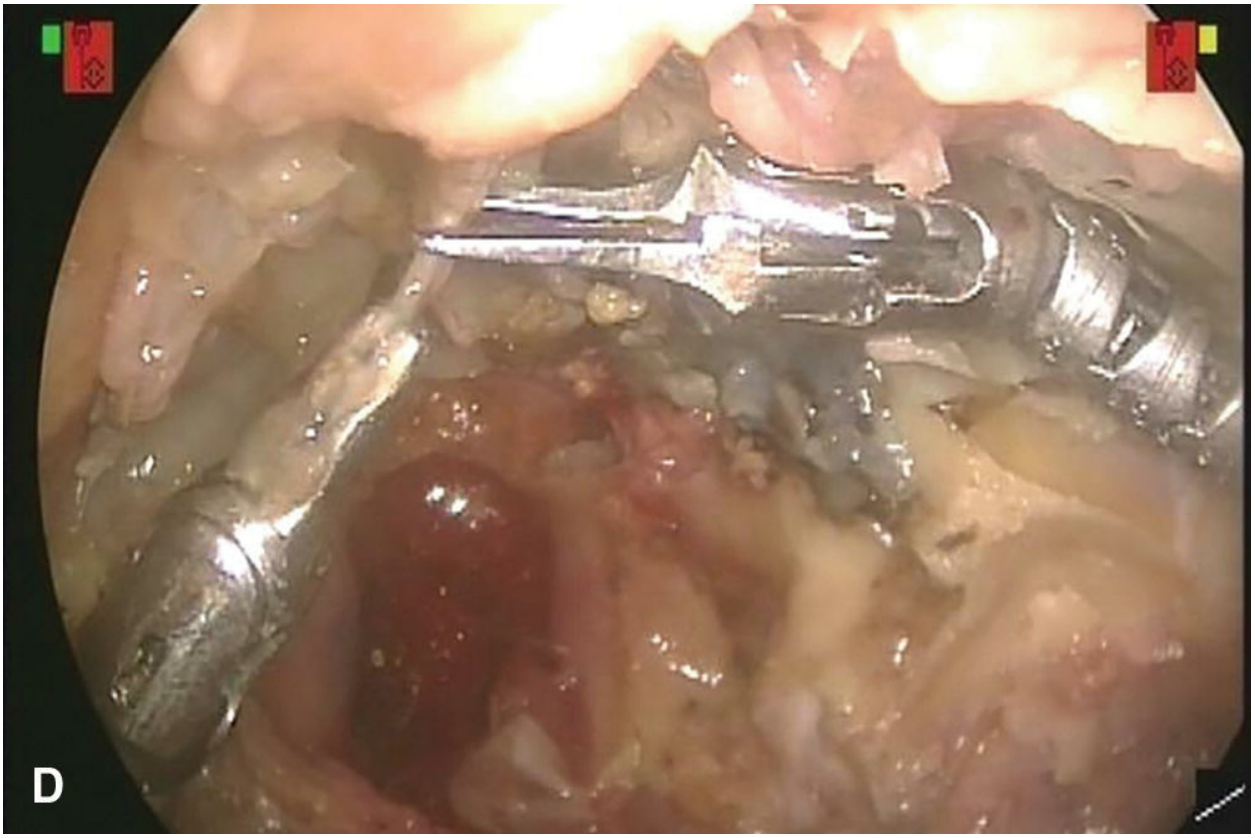
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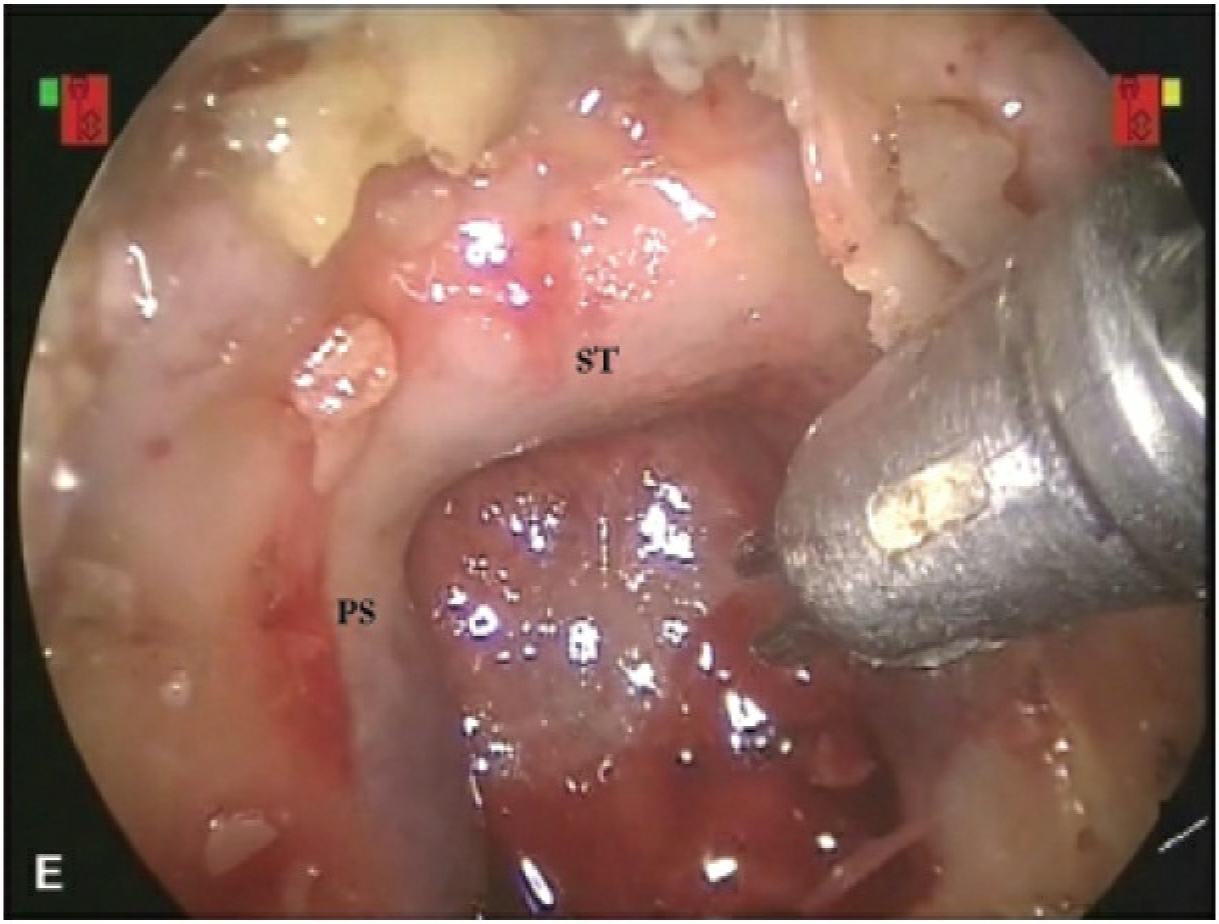
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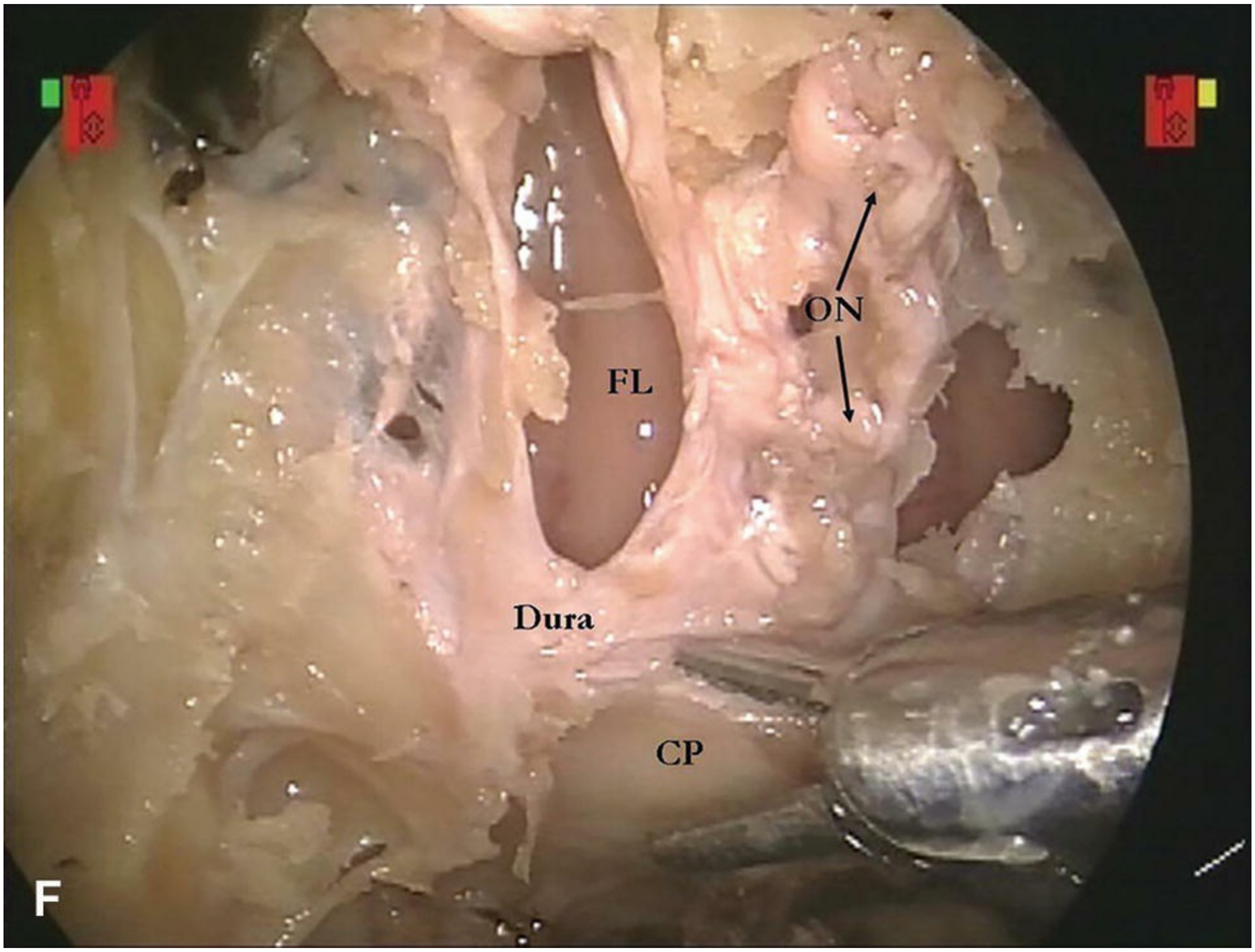

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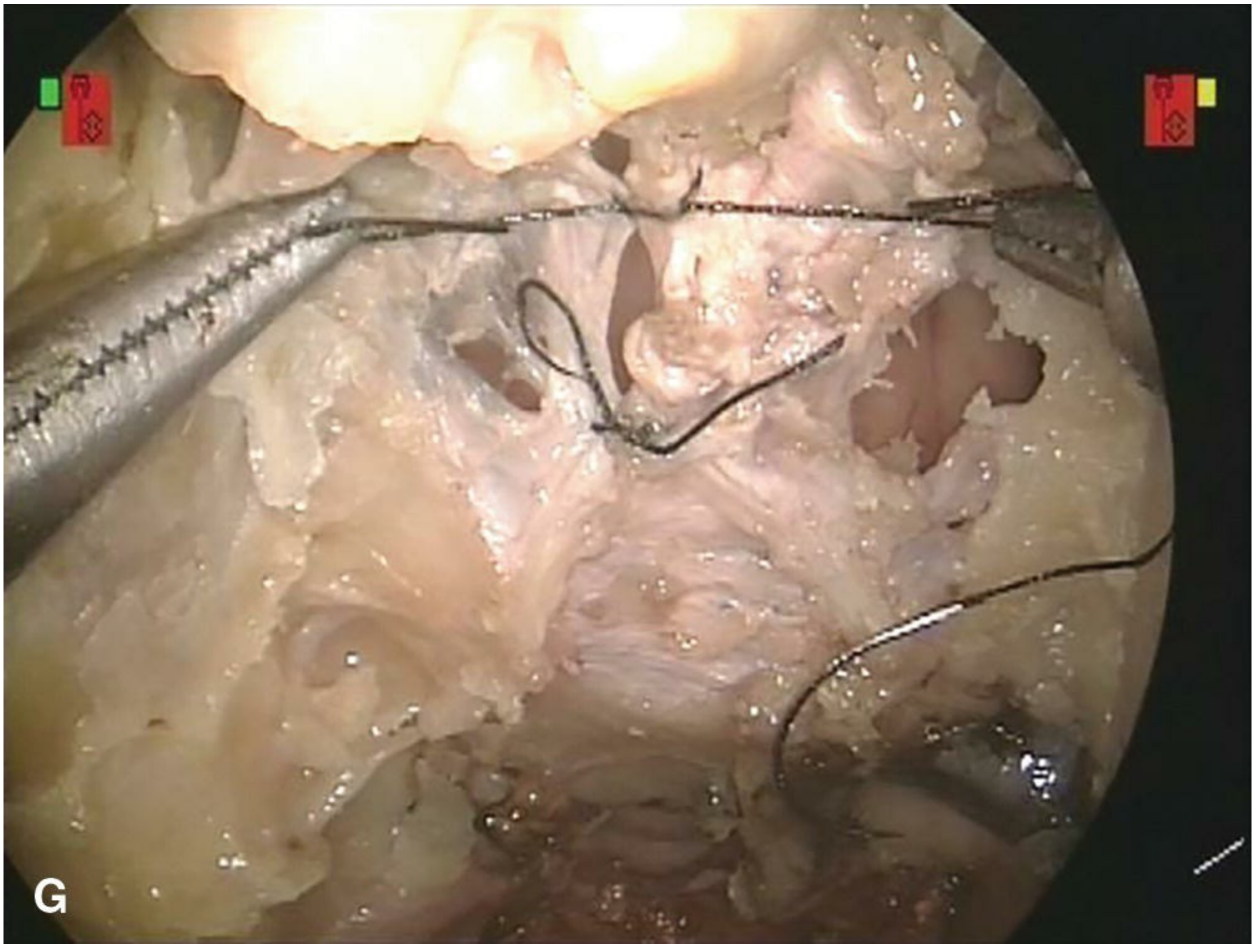
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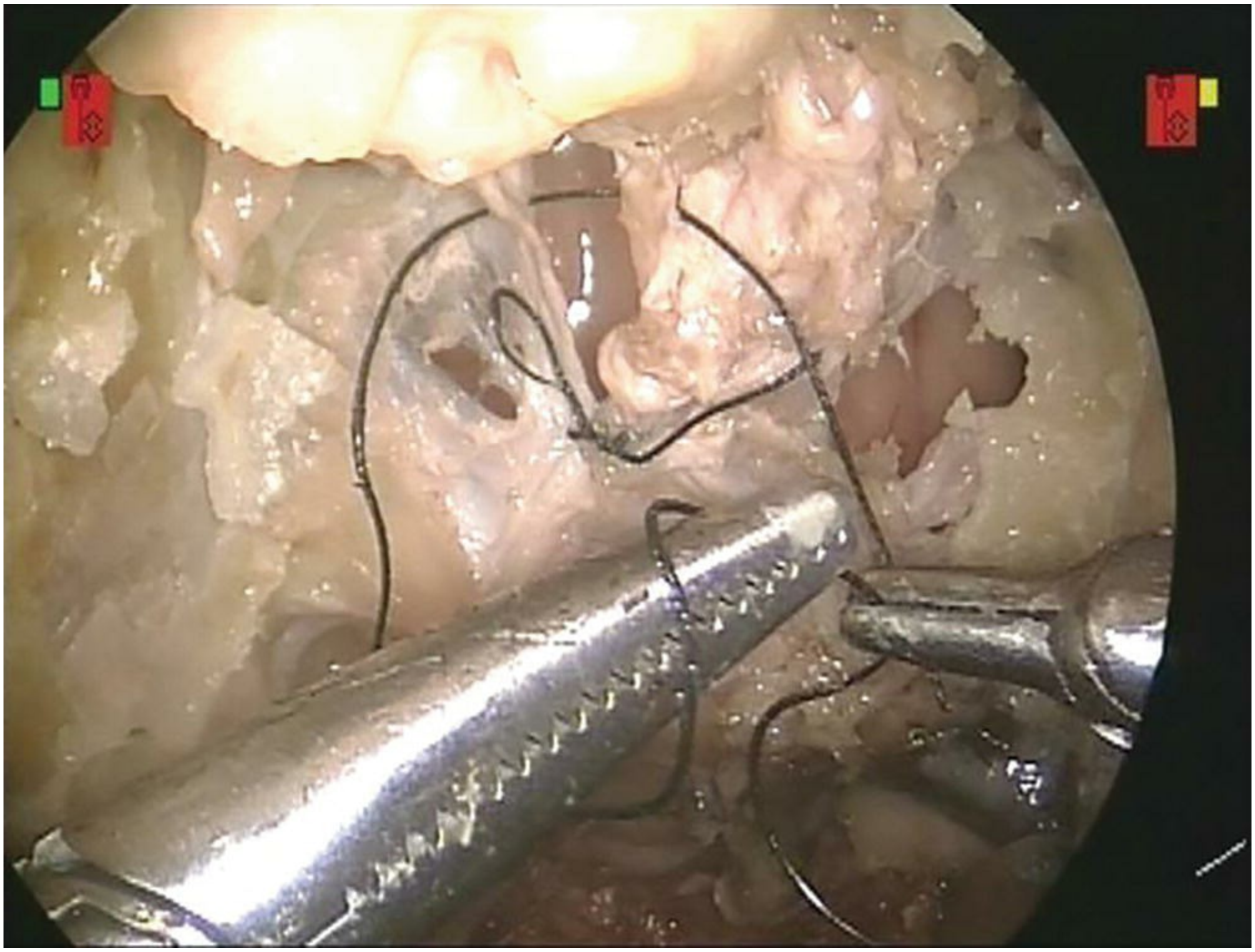


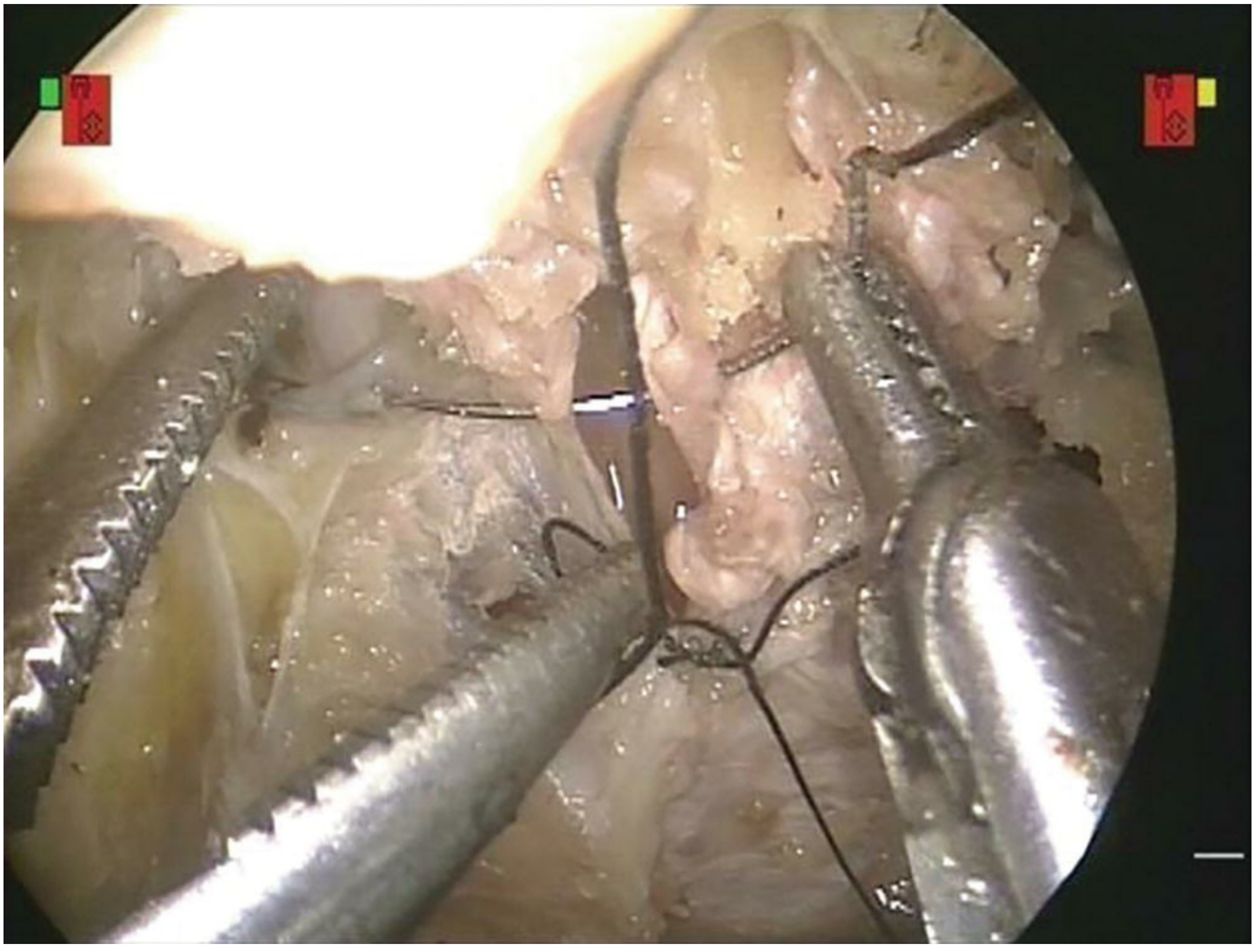


Figure 10.25. A: Soft tissue approach: bilateral sublabial incisions and soft tissue flap elevation. **B:** Bilateral anterior maxillary antrostomies. **C:** Robotic ports placement. The camera port is placed into the right nostril, and the right and left surgical arm ports through the respective anterior then middle antrostomies. **D:** Bimanual sharp dissection of the mucosa covering the fovea ethmoidalis and cribriform plate. **E**: Wide sphenoidotomy with excellent access to the sella turcica (ST) and parasellar region (PS). **F:** The cribriform plate (CP) is removed bilaterally, and the cut edges of the olfactory nerves (ON) are shown. The dura is incised or resected to expose the inferior surface of the frontal lobes (FL) intracranially. **G:** Dural repair. Suturing the dural edges, making a loop, and tightening the knot.

Transfacial Approaches: Lateral Rhinotomy and Weber-Fergusson.

Transfacial approaches are the most commonly used surgical approaches for

resection of locally advanced sinonasal tumors. They allow adequate exposure of the nasal cavity, maxillary sinus, pterygopalatine fossa, pterygoid plates, ethmoid sinuses, medial and inferior orbital walls, sphenoid sinus, nasopharynx, clivus, and the medial aspect of the infratemporal fossa.

The *lateral rhinotomy* is the standard incision for exposure of sinonasal tumors through a transfacial approach[44] (**Fig. 10.26**). It can be used alone, or various extensions of the basic incision may be added for further exposure depending on the extent of tumor. The *Weber-Fergusson* incision adds a lip-splitting and subciliary incision for added exposure of the maxillary bone. We prefer to extend the lateral rhinotomy toward the medial brow, a Lynch-type extension, and avoid the subciliary incision of the classic Weber-Fergusson to minimize eye lid complications as will be discussed further under the section on "total maxillectomy."

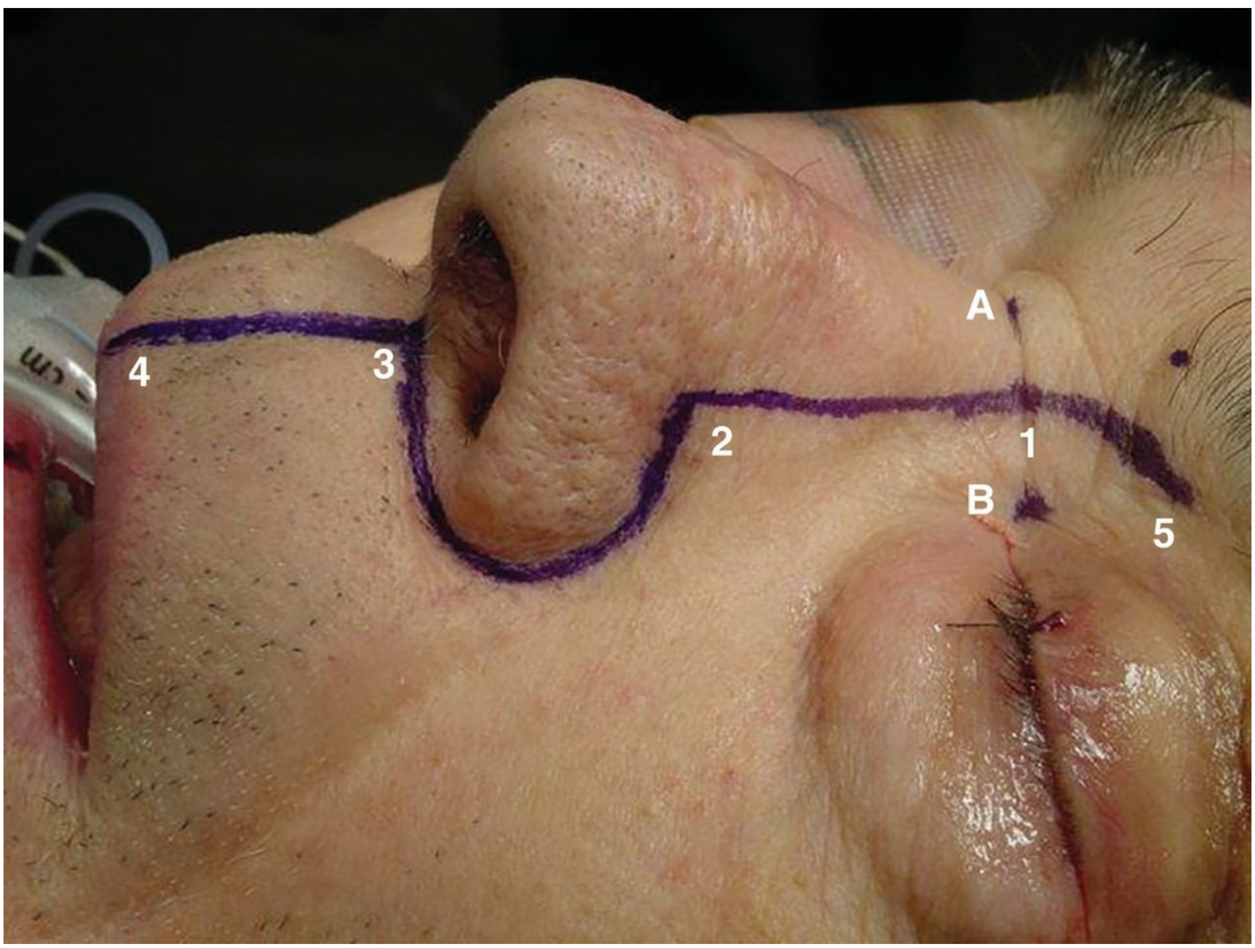
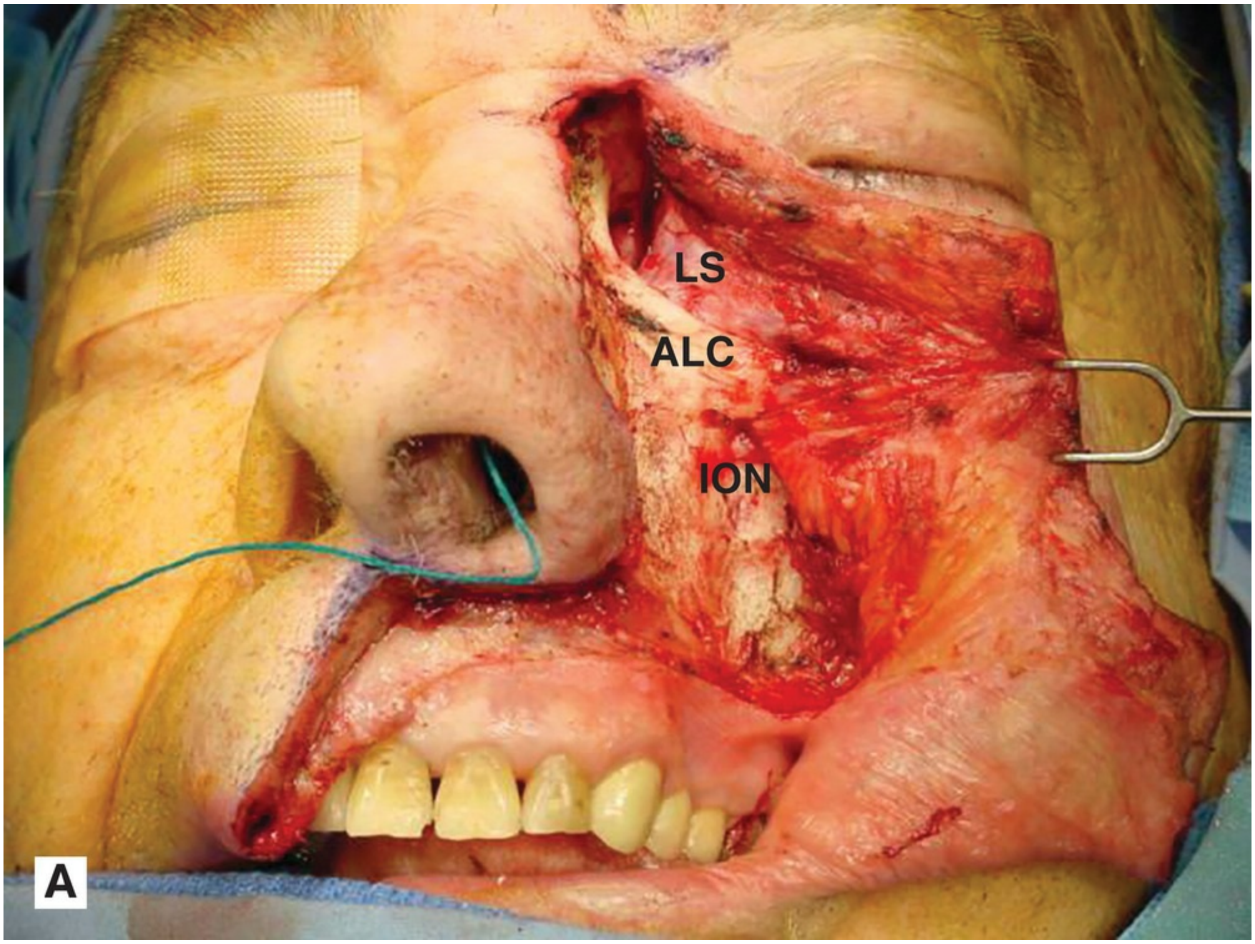


Figure 10.26. Lateral rhinotomy incision (*1*, *2*, *3*) and its extensions (*4*, *5*). The basic lateral rhinotomy incision is outlined by connecting three surface

points. The first point (*1*) is marked half way between the nasion (*A*) and the medial canthus (*B*). The second point (*2*) is where the alar crease begins, and the third point (*3*) is at the base of the columella. The basic incision provides adequate exposure for a medial maxillectomy. The basic incision may be extended to include a lip-splitting extension (*4*) or a “Lynch”-type extension (*5*) if further exposure is necessary. The extended incision provides adequate exposure for a total maxillectomy. A temporary tarsorrhaphy protects the ipsilateral globe.

The basic lateral rhinotomy incision provides adequate exposure when performing a medial maxillectomy. Elevation of the soft tissues of the cheek is done in a subperiosteal plane over the maxilla and around the inferior orbital nerve (**Fig.** 10.27**A**). The attachment of the medial canthal tendon to the nasal bone is released. The periorbita is elevated over the medial orbital wall exposing the lacrimal crest, the lamina papyracea, and the frontoethmoidal suture. This suture serves as a landmark for the position of the floor of the anterior cranial fossa, and when followed posteriorly, leads to the anterior and posterior ethmoidal foramina. The anterior and posterior ethmoidal arteries are cauterized with the bipolar electrocautery, clipped or ligated, and transected (**Fig. 10.27B**). The optic nerve is located 4 to 5 mm posterior to the posterior ethmoidal artery. The orbital floor should be dissected as far lateral as the inferior orbital fissure. The lacrimal sac is identified in its fossa between the anterior and posterior lacrimal crests. If a medial maxillectomy is performed, the lacrimal sac is elevated from the fossa, the lacrimal duct transected, and the sac marsupialized into the nasal cavity to provide adequate drainage of the lacrimal system and to prevent stenosis (**Fig. 10.27C**).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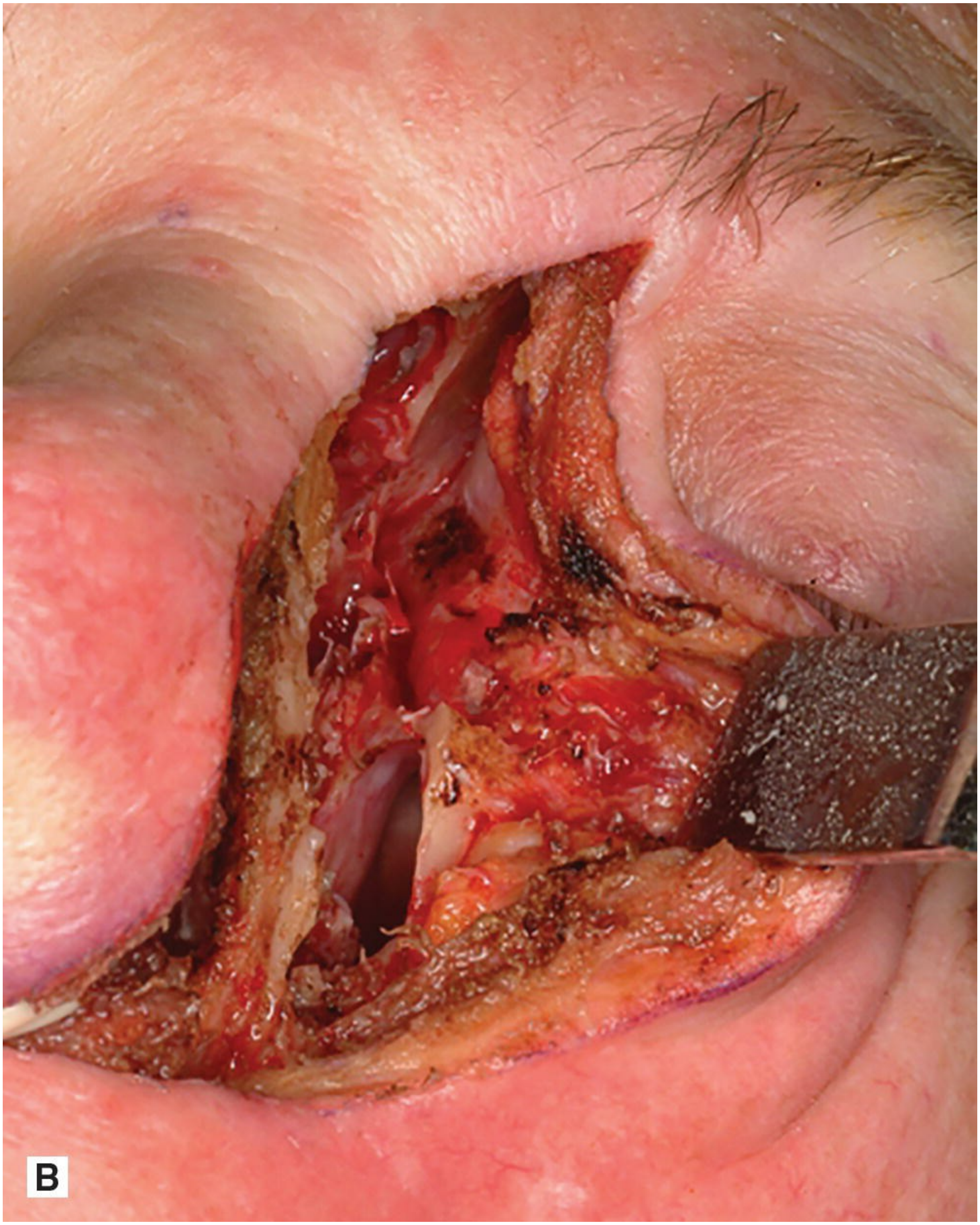
ALC
ION
A



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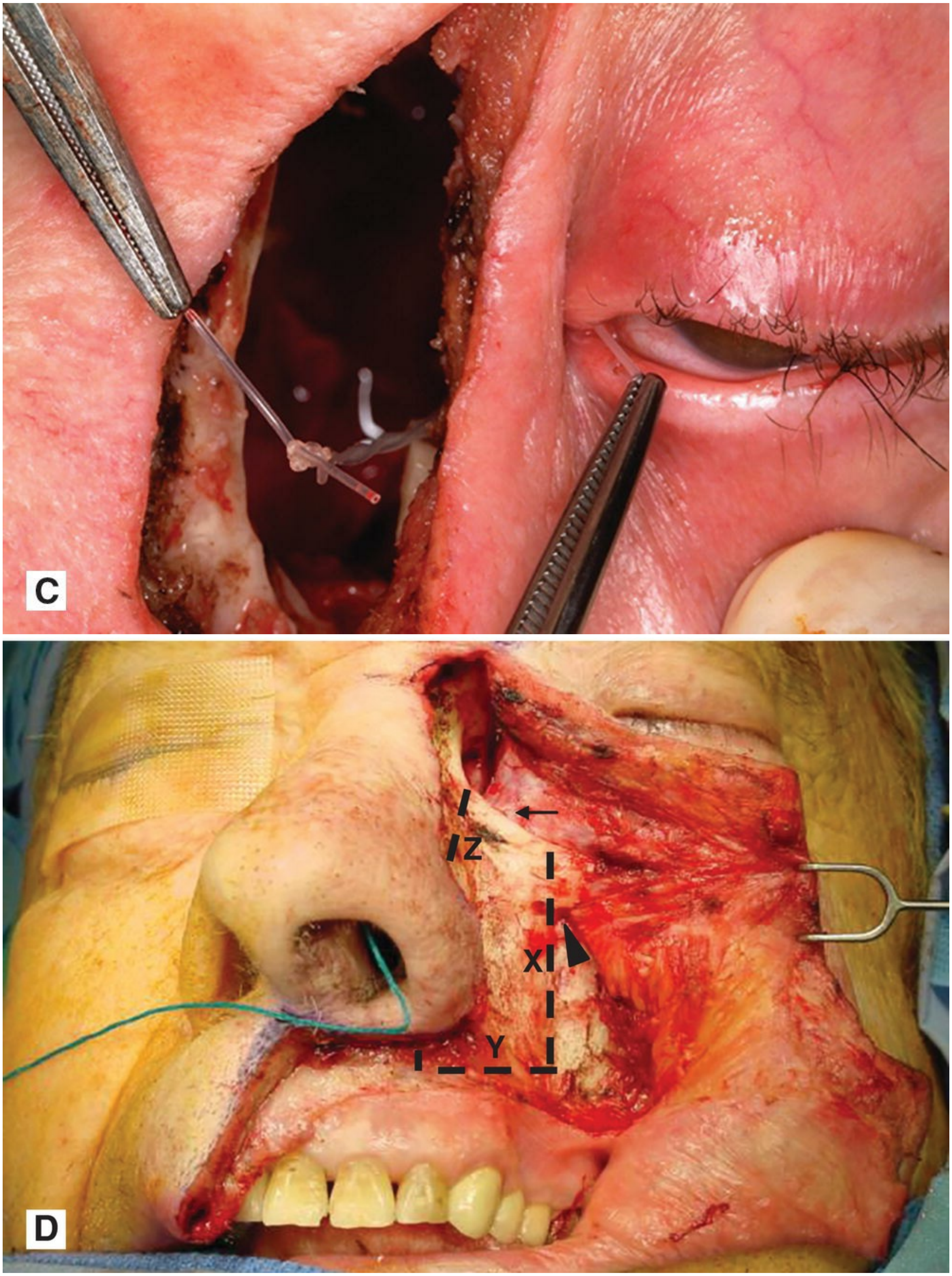
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Figure 10.27. A: Elevation of the soft tissues of the cheek is done in a subperiosteal plane over the maxilla and around the inferior orbital nerve (ION). The periorbita is elevated over the anterior lacrimal crest (ACL) to expose the lacrimal sac (LS). **B:** Dissection of the medial periorbita over the lamina papyracea reveals the anterior ethmoid artery at the level of the frontoethmoid suture line, which marks the level of the anterior cranial floor. The artery is coagulated by bipolar electrocautery, clipped or ligated, and then transected. **C:** After the lacrimal sac is transected, it is marsupialized into the surgical cavity as a dacryocystorhinostomy. Silicone stents are placed through the upper and lower canaliculi and brought into the nasal cavity to prevent postoperative epiphora. These stents are removed in about 3 to 6 months. **D:** Medial Maxillectomy. Osteotomies: (*X*) vertically medial to the infraorbital foramen (*arrowhead*), (*Y*) horizontally above the level of dental roots and into the pyriform aperture, and (*Z*) obliquely along the nasomaxillary suture line. If the lateral nasal wall is to be resected, the lacrimal sac (*arrow*) is transected and marsupialized into the nasal cavity. **E:**Postoperative appearance of a lateral rhinotomy incision.

Transoral or Transpalatal Approach.

The transoral approach is ideally suited for exposure of the palate, alveolar ridge, and inferior maxilla. The approach utilizes a combination of the sublabial gingivobuccal sulcus incision, and a palatal incision. It is most commonly applied for inferior (infrastructure) maxillectomy. It can also be used for tumors limited to the upper alveolar ridge and hard palate.

The transpalatal approach is usually performed by elevating a posteriorly based palatal flap and removal of the posterior aspect of the hard palate to expose the posterior choanae and nasopharynx. It allows adequate exposure for excision of limited tumors of the posterior nasal cavity and nasopharynx such as juvenile nasopharyngeal angiofibroma.

Midfacial Degloving and Sublabial Approaches.

The midfacial degloving approach is most commonly used in the management of large benign lesions of the sinonasal region and skull base such as juvenile nasopharyngeal angiofibroma, for selected malignancy in this area and to afford access to the nasopharynx and infratemporal fossa. The main advantage of the “degloving” approach is that an external facial incision is avoided. Another advantage is providing simultaneous exposure to the inferior and medial maxilla, bilaterally (**Fig. 10.28**). This is particularly helpful when approaching tumors with bilateral involvement of the nasal cavity and maxillary sinus. A major disadvantage, however, is the limited superior and posterior exposure and the need for constant retraction of the soft tissue envelope for continued adequate exposure.

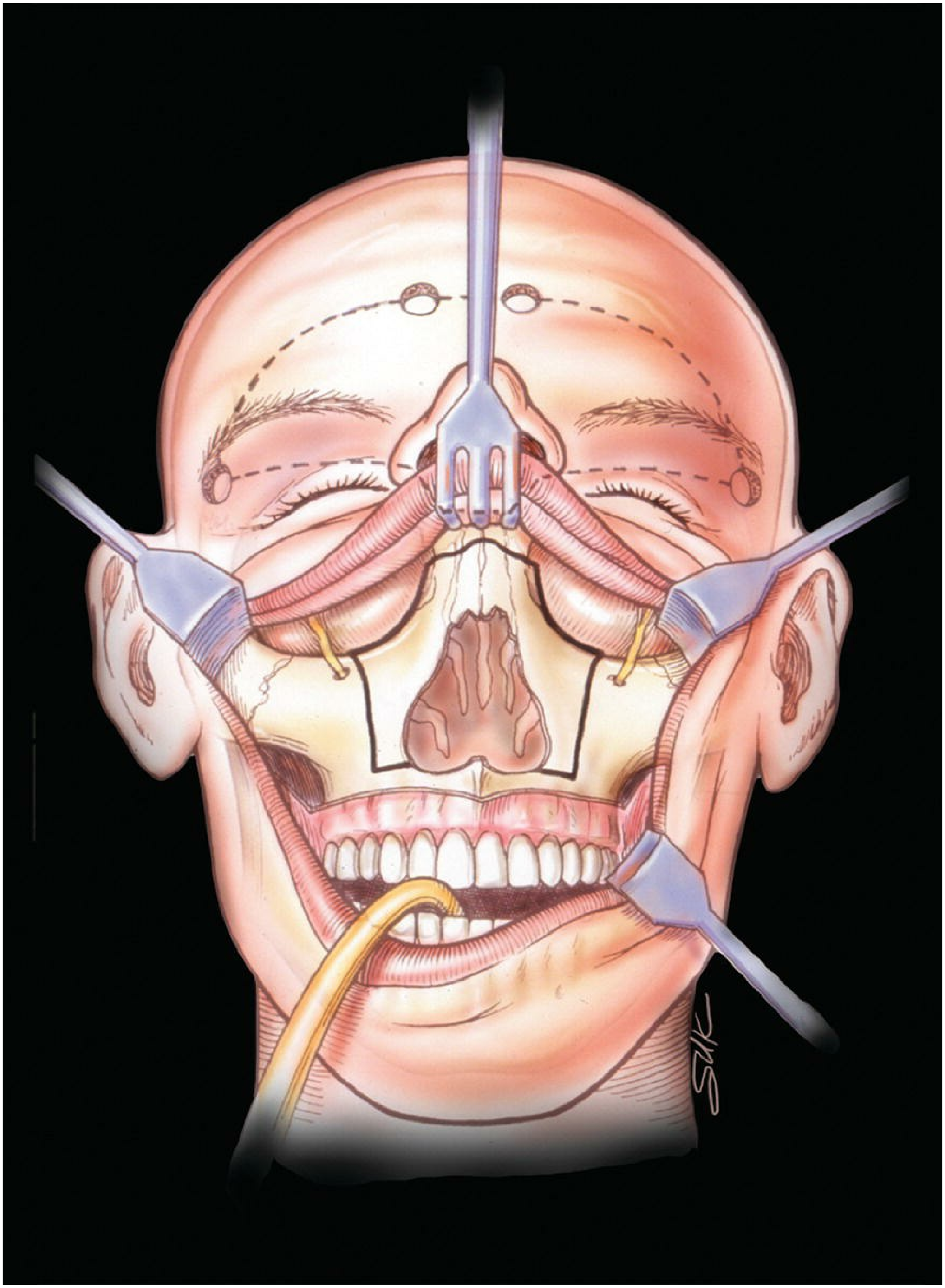
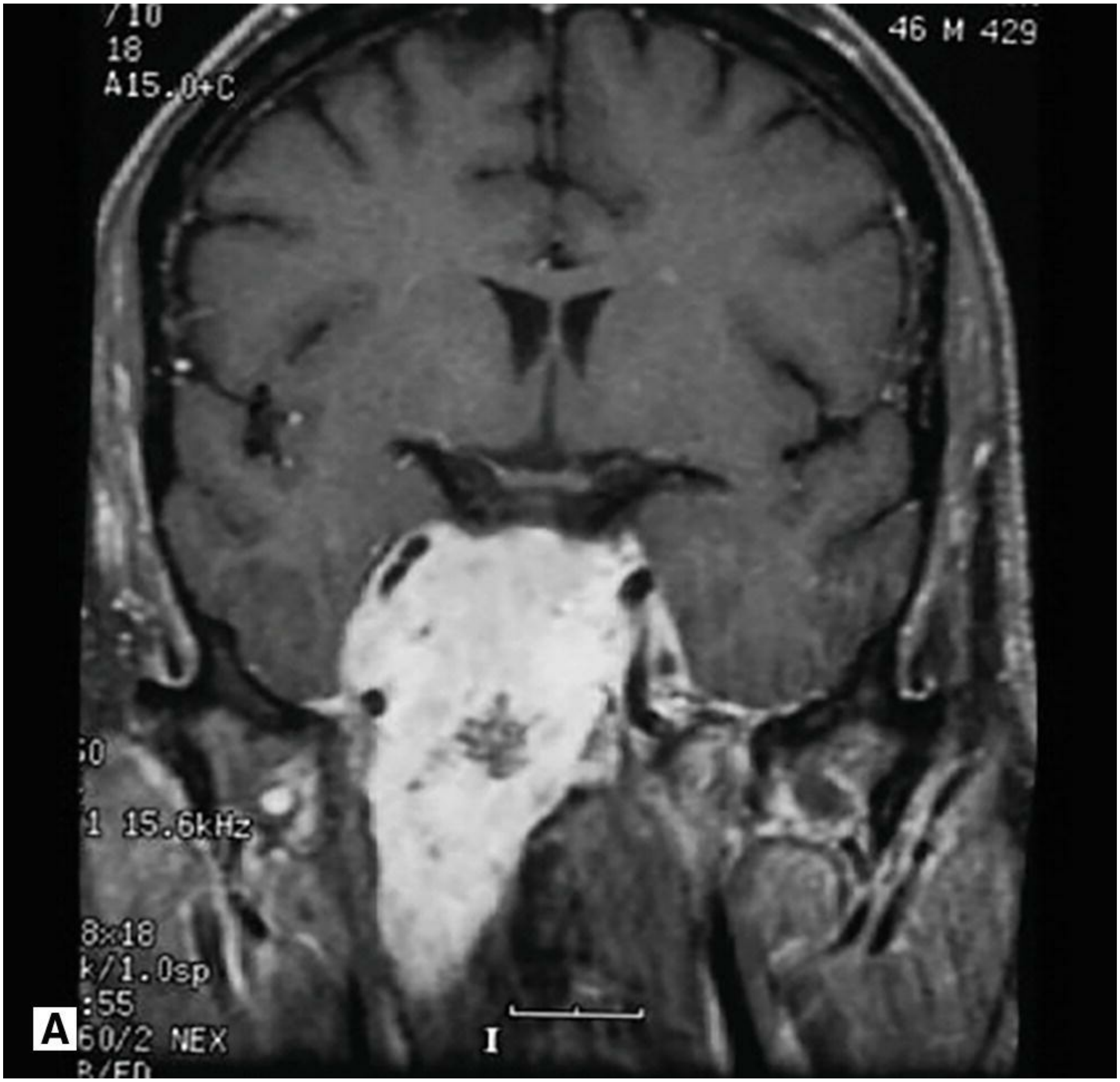


Figure 10.28. Sublabial "facial degloving" approach. In addition to avoiding facial incisions, it has the advantage of providing bilateral access to the medial and inferior maxillary segments.

The midfacial degloving approach requires a basic level of proficiency and understanding of closed rhinoplasty incisions. It involves a complete transfixion incision of the membranous septum. This is joined endonasally with a bilateral intercartilaginous incision, with soft tissue elevation over the nasal dorsum as far superior as the nasal root. The nasal skeleton is therefore "degloved" from overlying soft tissues as far lateral as the pyriform aperture. A gingivobuccal incision extends bilaterally across the midline to both maxillary tuberosities laterally. Subperiosteal dissection is continued cephalad over the face of both maxillae. The dissection joins the nasal degloving using sharp dissection over the pyriform aperture attachments (Fig. 10.28).

The sublabial approach may also be used to access tumors of the sphenoclival region such as chordoma, particularly if the lesion extends lower than the horizontal plane of the palate, for example, the lower third of the clivus and craniovertebral junction (**Fig. 10.29**). A Le-Forte I osteotomy is done, and the maxilla is displaced inferiorly after posterior osteotomies separate the maxilla from the pterygoid plates. We prefer a combination of unilateral or half a Le-Forte I osteotomy with a median or paramedian palatal osteotomy for better displacement of the maxilla inferiorly and laterally. This offers wider exposure because it avoids the cantilever effect of the posterior maxilla upward restricting exposure when the anterior maxillary segment is displaced inferiorly when the bilateral (complete) Le-Forte osteotomy is used.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18
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Ex:2800
Se:9/10
Im:8/16
TR:366
15.6kHz
1.0thk/1.0sp
IRP
B


S64
Ex:2904
Se:5/8
Im:6/20
Cor A10.6+C
10:12
R
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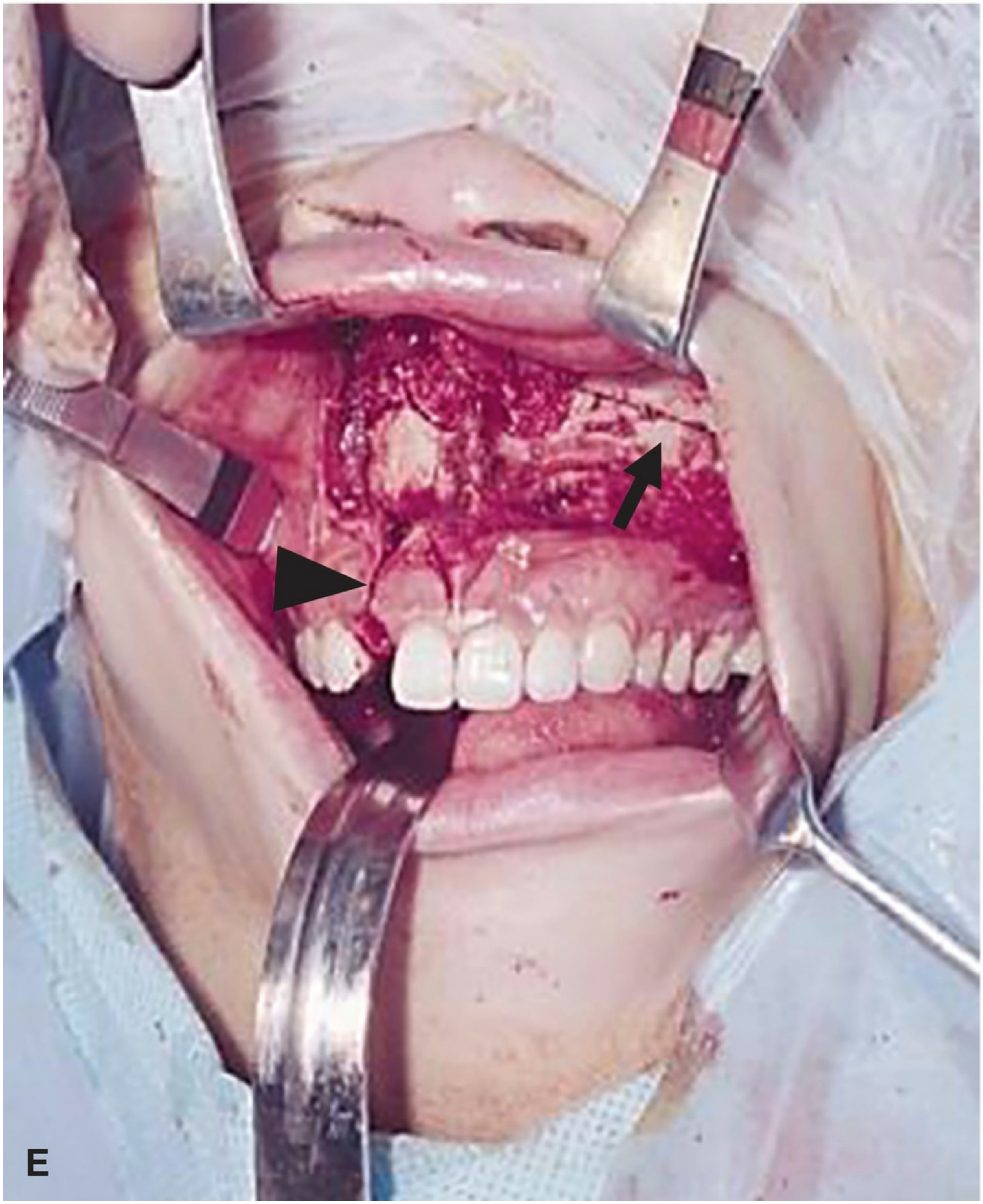
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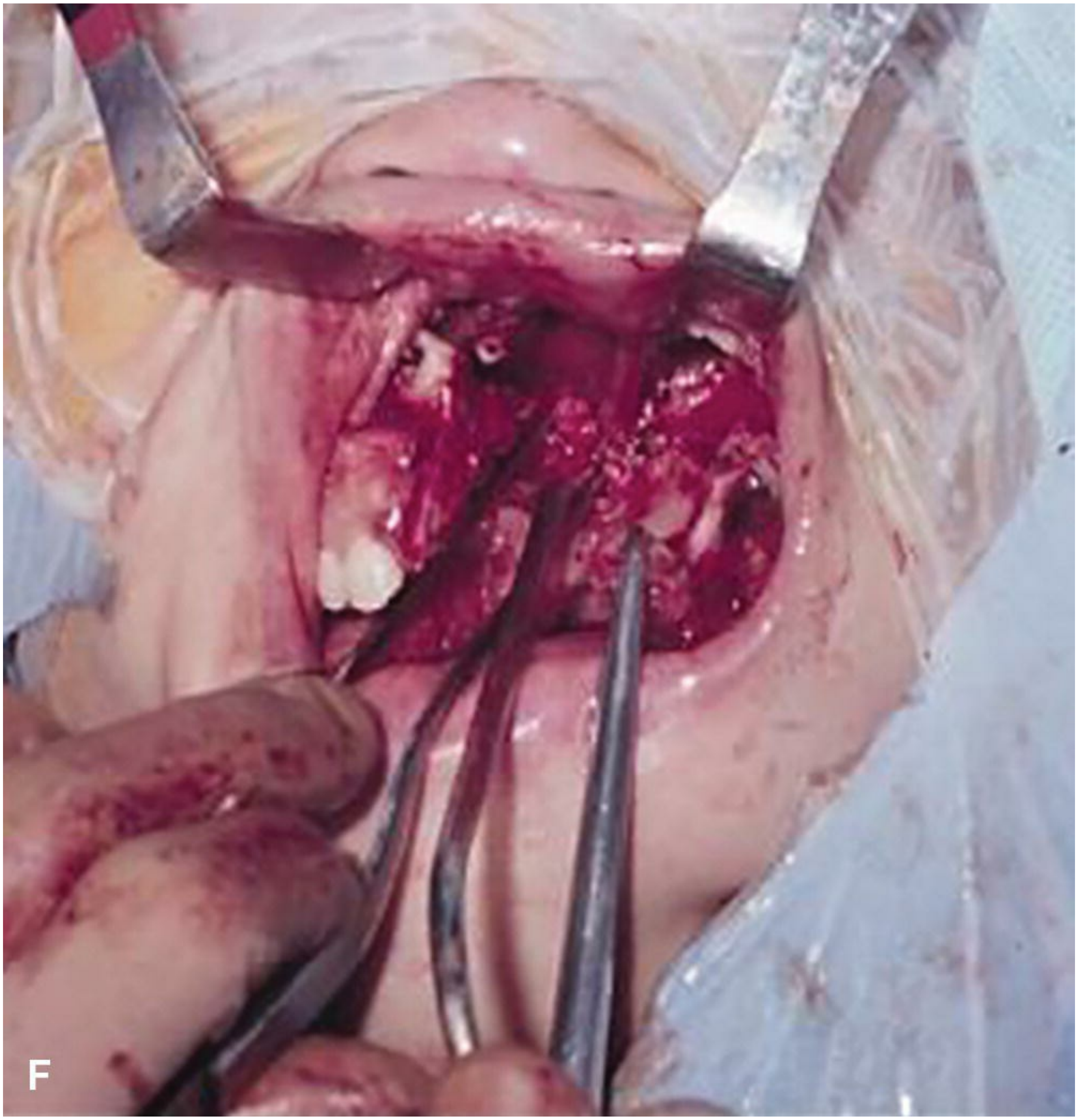
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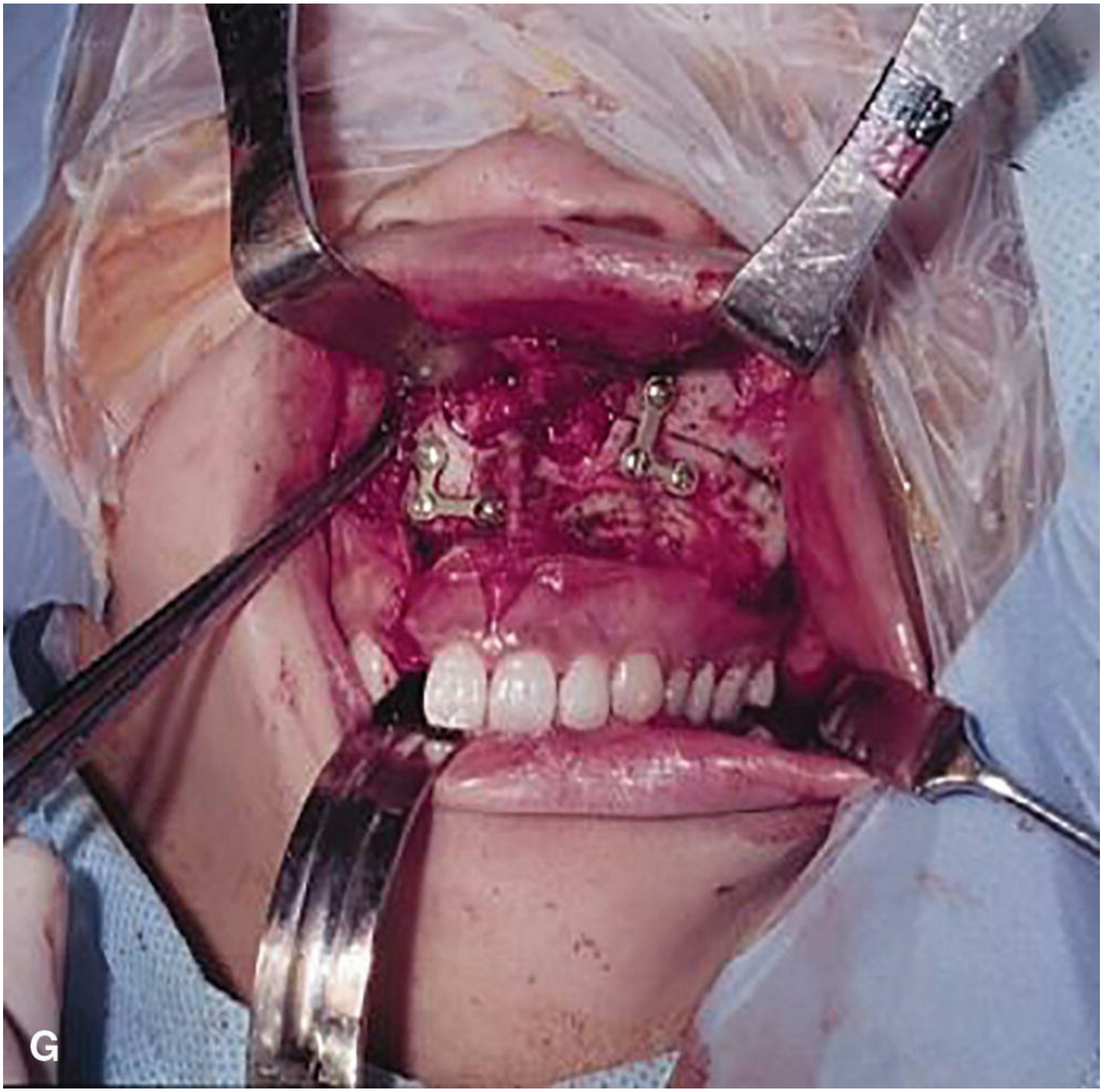


Figure 10.29. Sublabial approach and inferior maxillotomy for access to sphenoclival region. Preoperative **(A, B)** and postoperative **(C, D)** coronal and sagittal MRI of a patient with clival chordoma. **E:** LeFort I osteotomy (*arrow*) is done on one side only and connects the pyriform aperture. A second paramedian palatal osteotomy is performed (*arrowhead*). **F:** Inferior displacement of the maxilla (maxillotomy) to expose the sphenoid sinus, nasopharynx, and clivus. **G:** Rigid fixation of the maxillary segments using "pre-registered" titanium microplates to avoid any malocclusion.

Extent of Resection

Medial Maxillectomy.

The most common indication for medial maxillectomy is in the treatment tumors of the nasal cavity, lateral nasal wall, and medial maxillary sinus (Fig. 10.18). Medial maxillectomy includes removal of the lateral nasal wall and the medial maxillary segment bounded laterally by the infraorbital nerve. In addition, a complete sphenoethmoidectomy is usually performed.

The incision most commonly used for exposure is the lateral rhinotomy (Fig. 10.26). Alternatively, a midfacial degloving may be used and is preferable if bilateral medial maxillectomy is needed (Fig. 10.28). Endonasal endoscopic medial maxillectomy and sphenoethmoidectomy may be also performed for appropriately selected tumors (Fig. 10.22).

If the lateral rhinotomy is performed and soft tissue exposure is completed as discussed in the previous section, *osteotomies* are done as shown in Figure 10.27D, and the anterior wall of the maxillary sinus above the level of dental roots and medial to the infraorbital nerve is removed. Lateral to the infraorbital foramen, the anterior wall antrostomy may be enlarged to expose the zygomatic recess of the antrum.

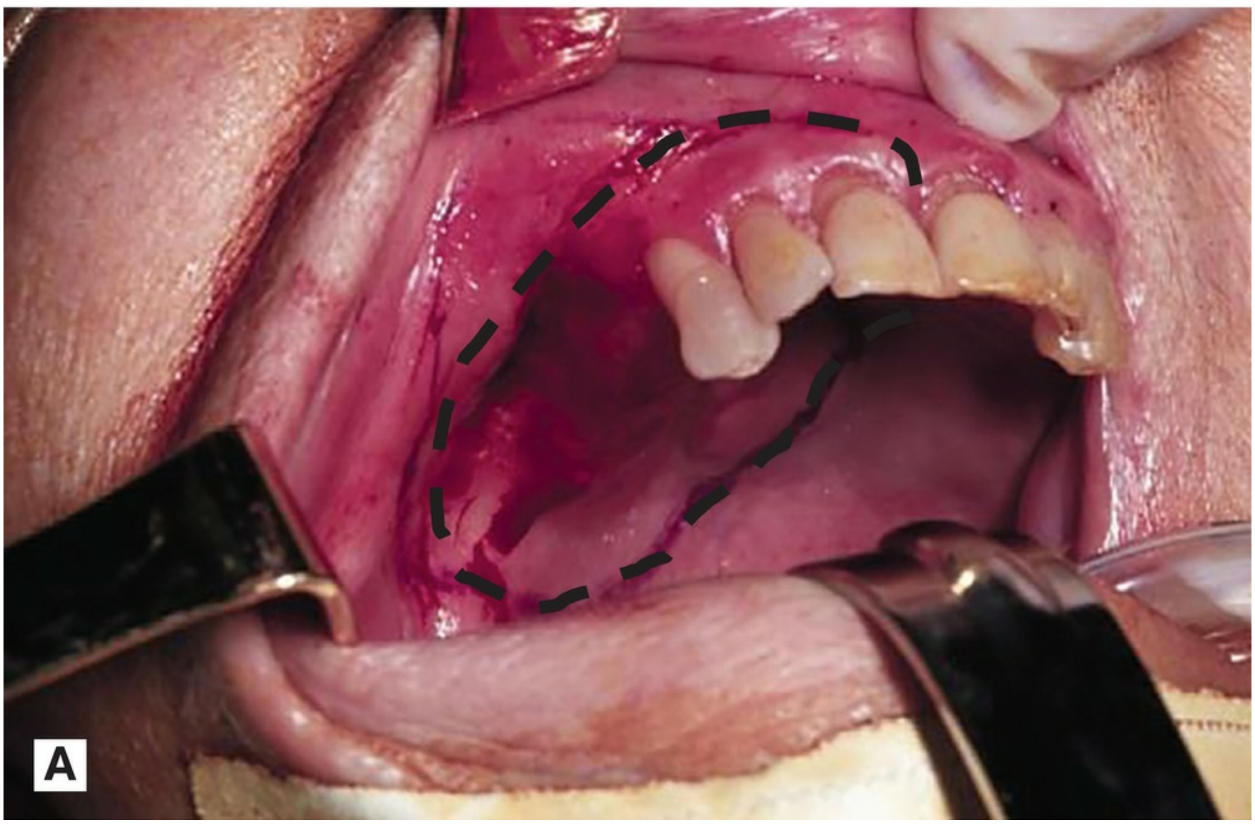
Resection of the lateral nasal wall begins with an inferior osteotomy along the nasal floor below the attachment of the inferior turbinate, starting at the pyriform aperture, and carried posteriorly to the posterior maxillary wall. With the orbit retracted laterally and protected with a malleable brain retractor, the lamina papyracea is identified and, if necessary, resected. A complete sphenoethmoidectomy is done, staying below the level of the frontoethmoidal suture to avoid injury to the floor of the anterior cranial fossa. The superior attachment of the middle turbinate is then transected along the roof of the nose. Posteriorly, the lateral nasal wall cuts are connected with right-angled scissors behind the turbinates. The specimen is thus delivered and examined for margins with frozen section control. If the tumor involves the nasal septum, it should be included in the resection specimen by adding appropriate septal cuts to allow for tumor-free margins.

Closure is begun by reattachment of the medial canthal tendon to the nasal bone in its anatomic position. Meticulous multilayered closure of the lateral rhinotomy is performed and usually results in excellent healing and acceptable postoperative appearance (Fig. 10.27E). If a sublabial approach is done, the mucosal incisions are closed with absorbable suture. Adequate

nonadherent nasal packing may be left for 1 to 2 days.

Inferior Maxillectomy.

This procedure involves resection of the inferior maxillary sinus below the plane of the infraorbital nerve. It is most commonly used for neoplasms of the alveolar process of the maxilla with minimal extension to the maxillary antrum. Similarly, lesions of the hard palate sparing the antrum can be treated by an inferior maxillectomy. A combination of sublabial and palatal incisions is usually used for exposure, and osteotomies are done around the lesion, ensuring an adequate margin of resection (**Fig. 10.30**). Alternatively, a midfacial degloving can be used for lesions crossing the midline and involving the inferior maxilla bilaterally.



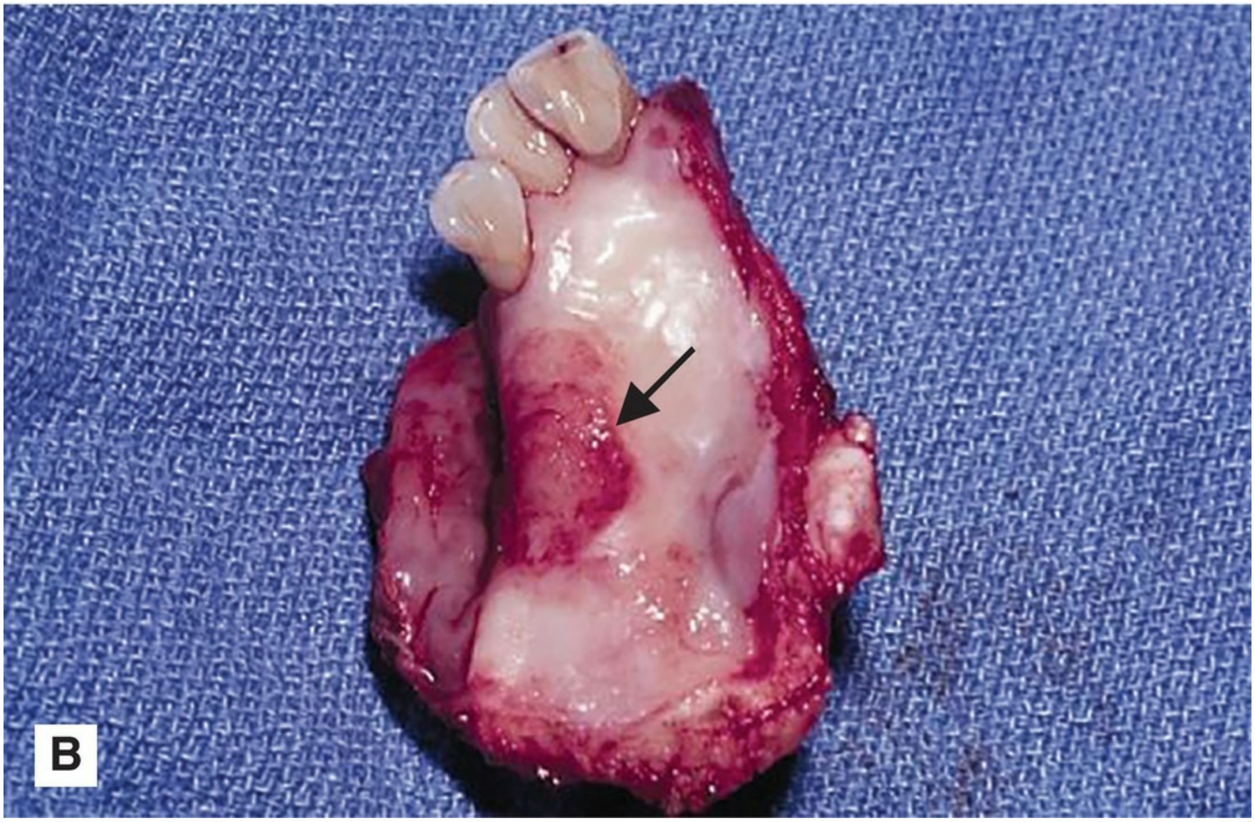
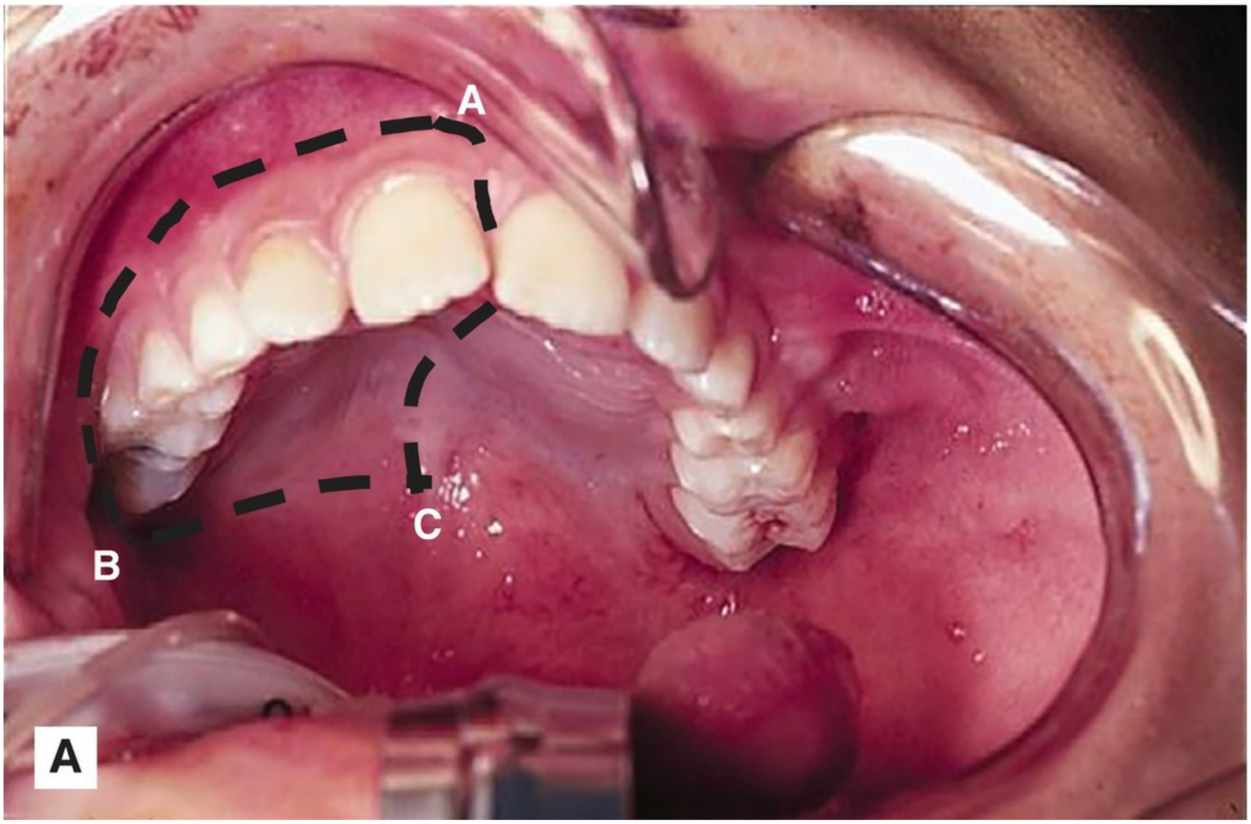


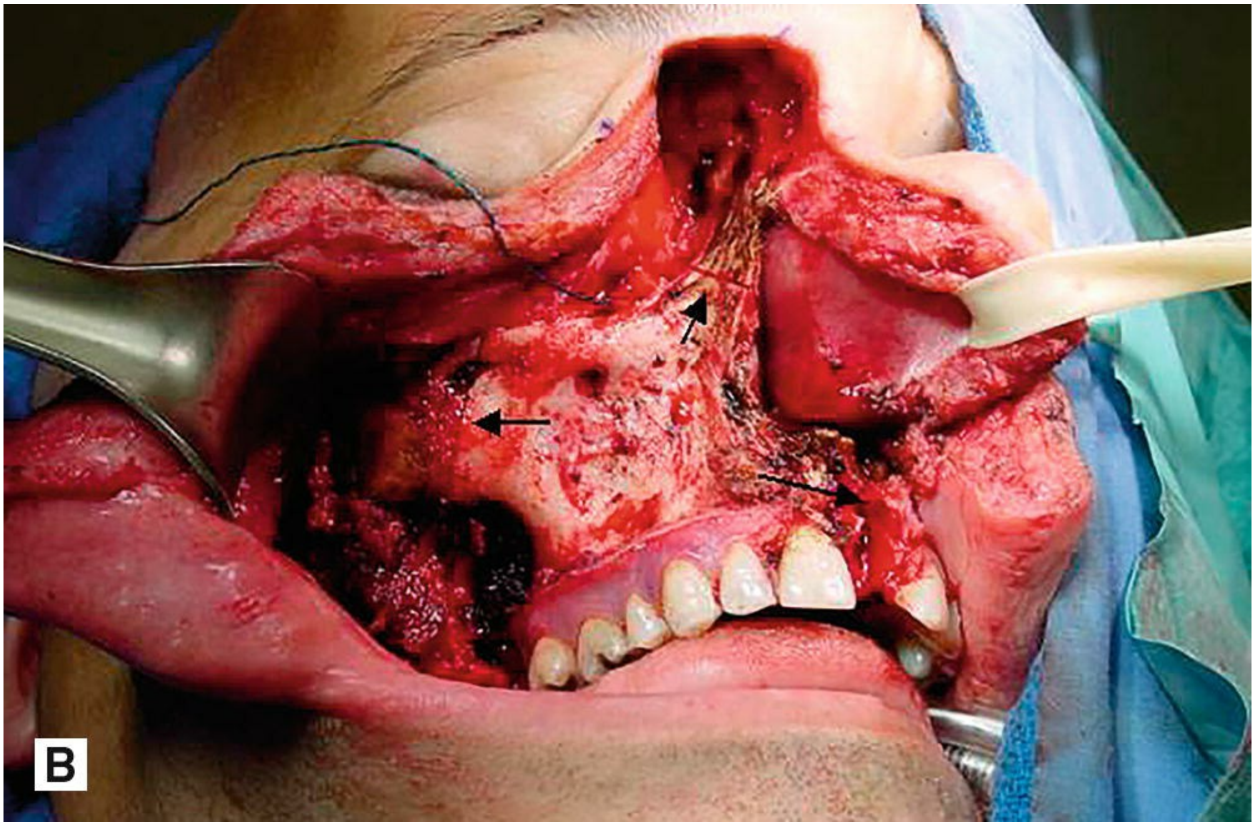
Figure 10.30. Inferior maxillectomy. Gingivobuccal and palatal incisions and osteotomies are done around the lesion as shown in **(A)**. If there is adequate space between the central incisors, the osteotomy may be performed using a micro-reciprocating saw in the interincisor space. Otherwise, the ipsilateral central incisor should be extracted and the osteotomy placed in the tooth socket in order to avoid loss of bony support to the remaining contralateral incisor. Inferior maxillectomy specimen **(B)** showing adequate surgical margins around an upper alveolar ridge carcinoma (*arrow*).

Total Maxillectomy.

If the extent of resection requires a total maxillectomy, the lateral rhinotomy incision may be extended by adding lip-splitting, gingivobuccal, and palatal incisions inferiorly. The lip-splitting incision, which may be done along the philtrum or in the midline, connects the lateral rhinotomy with the sublabial incision, thus allowing more lateral elevation of the facial flap. The gingivobuccal incision starts from the lip-splitting incision and extends as far laterally as the region of the first molar and over the lateral surface of the maxillary tuberosity. In patients undergoing total maxillectomy, a median or

paramedian palatal incision is performed over the hard palate extending from an interincisor space anteriorly, to the junction of the soft and hard palate posteriorly. The incision then continues laterally between the hard and the soft palate to curve posterolaterally around the maxillary tuberosity meeting the gingivobuccal incision (**Fig.** 10.31**A**).

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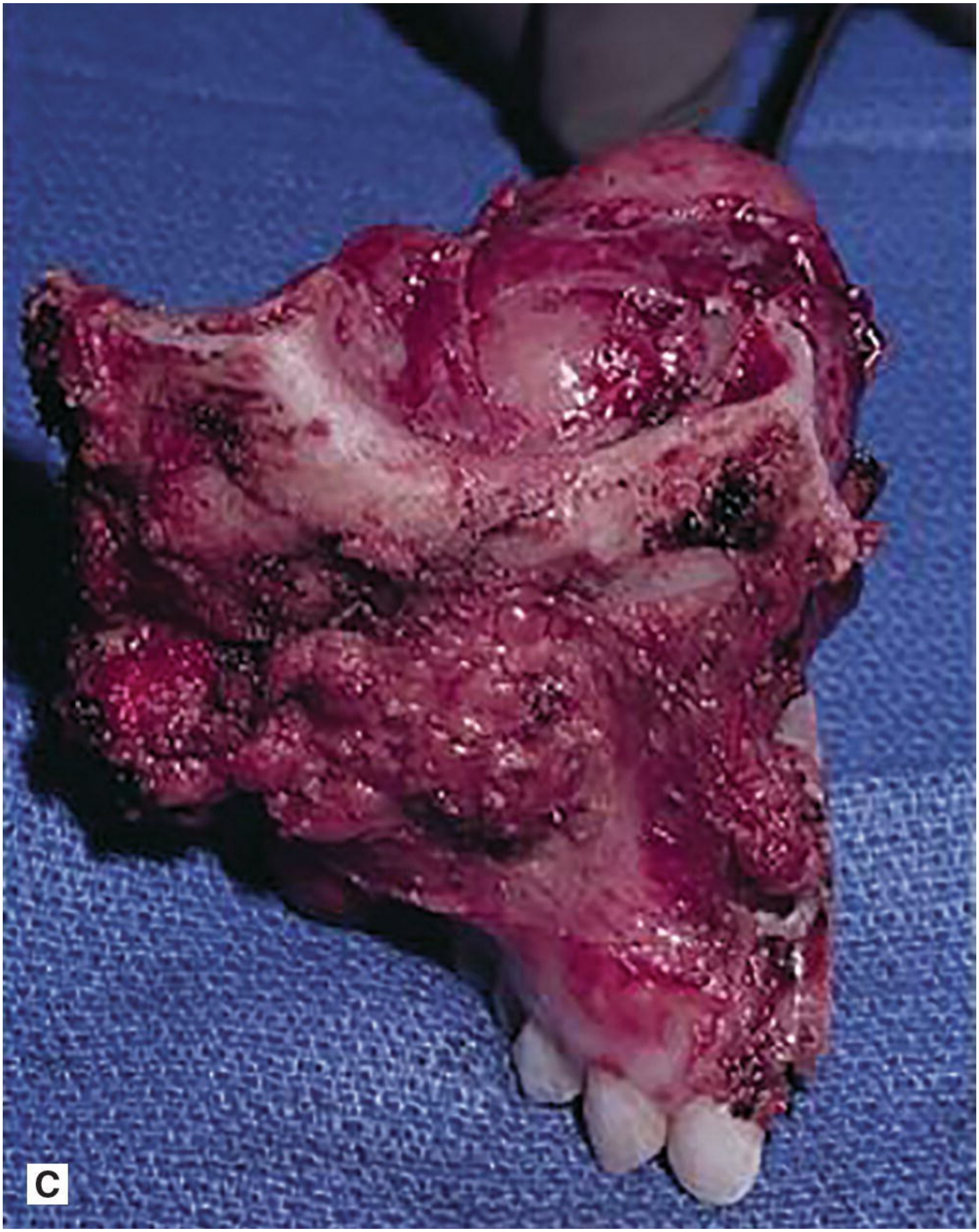


Figure 10.31. Total maxillectomy. **A:** Intraoral incisions. **B:** The exposure offered through an extended lateral rhinotomy shown in this figure is not less than that offered by the Weber-Fergusson incision. The advantage of the

former is avoiding a subciliary incision and its potential for lower eyelid ectropion and edema. Osteotomies have been performed as indicated by the *arrows*. **C:** En bloc resection specimen. Note tumor involvement of the orbital floor, which had to be resected. The tumor did not transgress the periorbita therefore the eye was preserved.

In patients undergoing total maxillectomy with orbital preservation, we prefer to extend the lateral rhinotomy superiorly beneath the medial brow rather than laterally through a subciliary incision used in the classic Weber-Fergusson approach (**Fig. 10.31B**). We described several advantages to this modification.[74] First, avoiding a subciliary incision eliminates any disruption to the lower lid skin–muscle–tarsus complex that minimizes lower eyelid complications, particularly ectropion and prolonged eyelid edema. Another advantage is avoiding trifurcation of the incision reducing the risk of skin breakdown at the medial canthal area. This is especially important for previously irradiated patients, who are more prone to develop medial canthal skin dehiscence. Similarly, because the vascularity of the thin lower eyelid skin is not affected with the extended lateral rhinotomy incision, patients who undergo orbital floor reconstruction with implants such as titanium mesh have less chance to develop wound breakdown and implant exposure. Although the extended lateral rhinotomy incision has several functional and cosmetic advantages, it does not compromise exposure and provides an adequate approach for a safe oncologic resection. The extension of the lateral rhinotomy incision beneath the medial eyebrow shifts the fulcrum of rotation of the soft tissue flap superiorly and laterally enhancing lateral exposure, which is not less from that obtained with a classic Weber-Fergusson incision (Fig. 10.31B). Transection of the infraorbital nerve allows even more lateral and posterior elevation of the soft tissues, to expose the entire maxillary bone as far lateral as its zygomatic extension and posteriorly to the pterygomaxillary fissure and over the pterygoid plates. Additionally, its postoperative cosmetic appearance is superior to the Weber-Fergusson incision (Fig. 10.27E).

Whichever incision is used, elevation of the facial flap is usually done in the subperiosteal plane. However, if the tumor has invaded the anterior wall of the maxillary antrum, a supraperiosteal plane is utilized. Occasionally, the cheek skin overlying the maxilla is included with the specimen, if it is involved with tumor. With the globe protected with a temporary tarsorrhaphy

stitch, the periorbita is dissected along the medial, inferior, and lateral orbital walls.

Lateral osteotomies are performed along the frontal and temporal processes of the zygoma (Fig. 10.31B). Medial osteotomies are done along the frontal process of the maxilla, and along the medial orbital wall just below the frontoethmoidal suture, extending posteriorly to the level of the posterior ethmoidal foramen. The medial and lateral osteotomies are then connected superiorly across the orbital floor along the inferior orbital fissure. Inferiorly, a midline sagittal osteotomy is made across the hard palate. The ipsilateral central incisor should be preserved, if possible, to enhance prosthesis retention. Finally, after the internal maxillary artery is identified at its entrance through the pterygomaxillary fissure, ligated, and transected, a posterior osteotomy is done to disarticulate the maxilla from the pterygoid plates. The maxilla is delivered by anteroinferior traction, whereas remaining soft tissue attachments are cut using a curved heavy scissors. Bleeding is usually encountered at this point and is controlled by temporary packing of the cavity, followed by electrocoagulation of bleeding mucosal surfaces or ligature of bleeding points. The pterygoid plexus of veins may be a source of persistent bleeding and can be managed by haemostatic figure-of-8 sutures and Surgicel packing. Bleeding is usually minimized if the internal maxillary artery is ligated before the posterior osteotomy is done along the pterygomaxillary fissure.

Total maxillectomy usually involves removal of the entire maxillary bone including the palate and the orbital floor (**Fig. 10.31C**). Preservation of the orbital floor (subtotal maxillectomy) or the palate (suprastructure maxillectomy) may be done if these structures are not involved by tumor. Depending on the extent of the lesion, resection may extend beyond the posterior wall to the pterygopalatine fossa and pterygoid plates. Perineural spread of tumor along V2 may be resected by following the nerve through foramen rotundum and into Meckel cave[75] (**Fig. 10.32**).

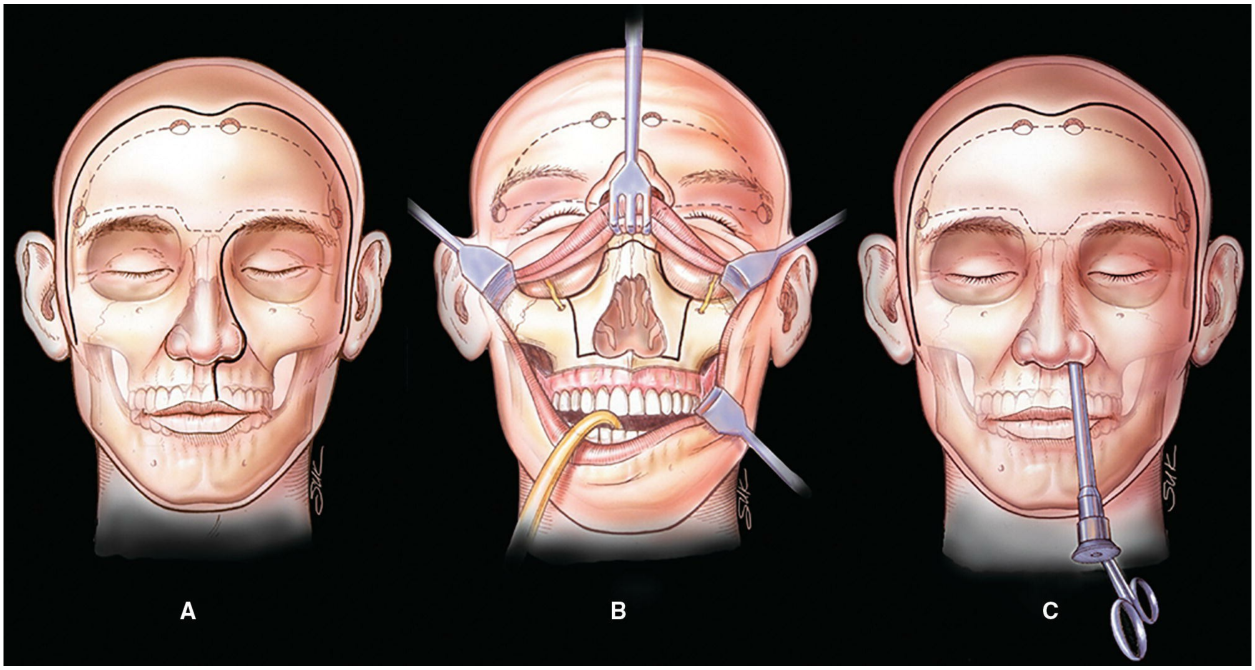


Figure 10.32. Anterior craniofacial resection: Extracranial approaches. In addition to the frontal craniotomy, the extracranial approach may be transfacial **(A)**, sublabial **(B)**, or endonasal **(C)**.

Craniofacial Resection.

Surgical resection of the *anterior* cranial base is commonly indicated for patients with sinonasal tumors involving the cribriform plate or fovea ethmoidalis. This is done, by definition, for most cases of ENB, as well as carcinoma of the ethmoid or maxillary sinuses approaching or involving the anterior cranial base (Fig. 10.16). Tumors transgress the cribriform plate either by direct bony invasion or by perineural spread along the filaments of the olfactory nerves. The dura of the anterior cranial fossa forms a barrier that delays, to a certain extent, brain invasion. Dural resection in patients with intracranial but extradural disease or patients with limited dural involvement often provides an adequate oncologic margin. However, malignant tumors that transgress the dural barrier and involve the underlying brain parenchyma are usually associated with poor prognosis.[53] However, even in some cases with limited frontal lobe involvement, anterior craniofacial resection may still be indicated for local control of the disease.

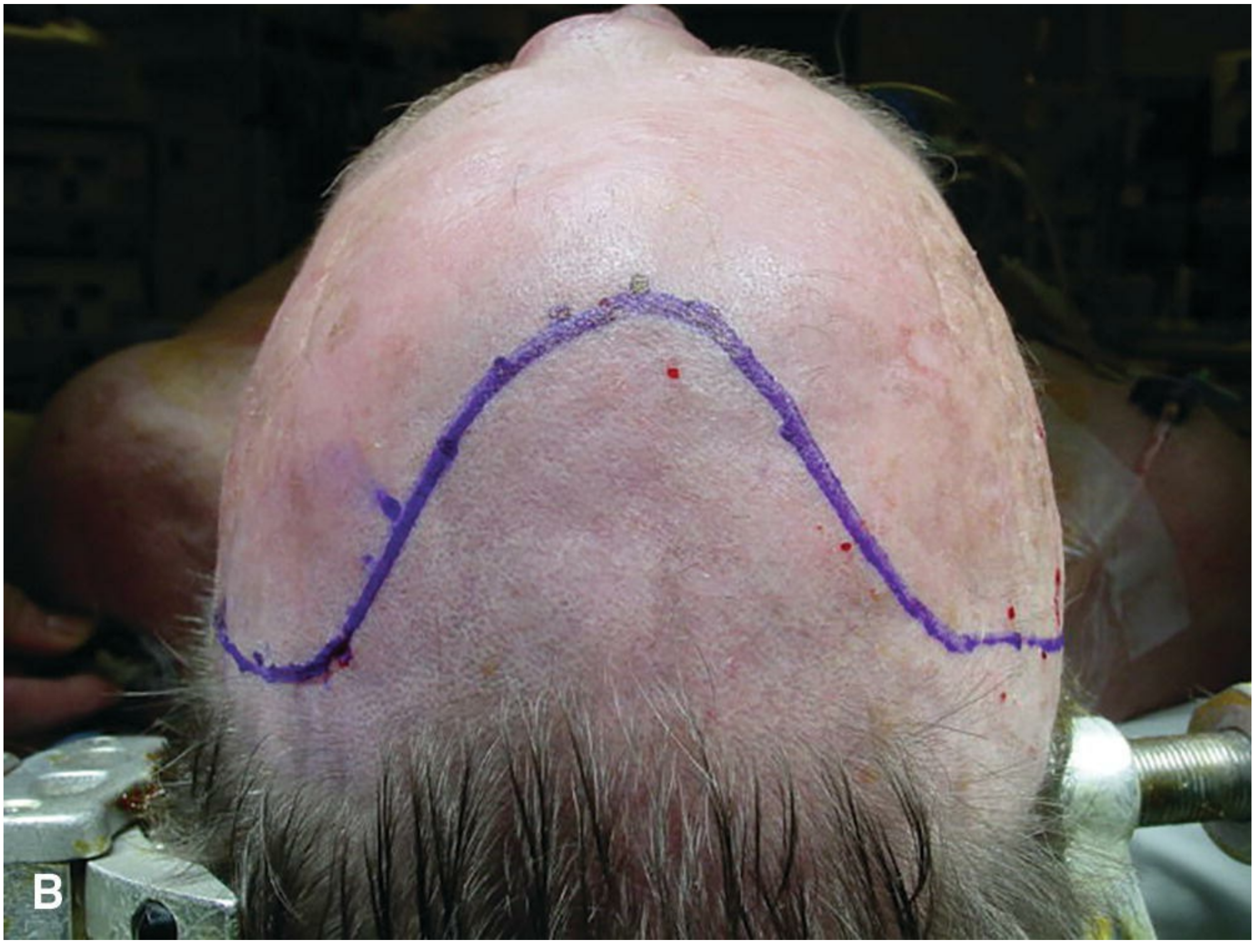
Resection of the floor of the *middle* cranial fossa is sometimes performed in patients with sinonasal tumors to achieve tumor-free surgical margins for

lesions extending to the roof of the infratemporal fossa or for those tumors that exhibit perineural spread along the branches of the trigeminal nerve to the gasserian ganglion, most commonly ACC.[44]

Craniofacial approaches combine extra- and intracranial access to the anterior and lateral skull base. Extracranial approaches may include transfacial, sublabial, or endonasal approaches as previously described[44] (Fig. 10.32).

The *bicoronal incision* starts in a preauricular crease anterior to the tragus. Careful dissection and preservation of the superficial temporal artery should be done. The scalp incision is extended in the coronal plane, staying behind the hairline along its entire course, to the contralateral preauricular region. We prefer to gently curve the incision anteriorly at the midline (**Fig.** 10.33**A and B**). The scalp flap is elevated in a subgaleal plane superficial to the pericranium between the superior temporal lines bilaterally. Lateral and inferior to the superior temporal lines, an incision is made through the superficial layer of the temporalis fascia 1 to 1.5 cm. posterior to the superior orbital rim and extends posteriorly parallel to the course of the zygomatic arch (**Fig. 10.33C**). Dissection proceeds at the plane of the deep layer of the temporalis fascia to preserve the frontal branch of the facial nerve, which is superficial to the fascia. The scalp flap is elevated anteriorly toward the superior orbital rims and posteriorly toward the vertex.


A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D
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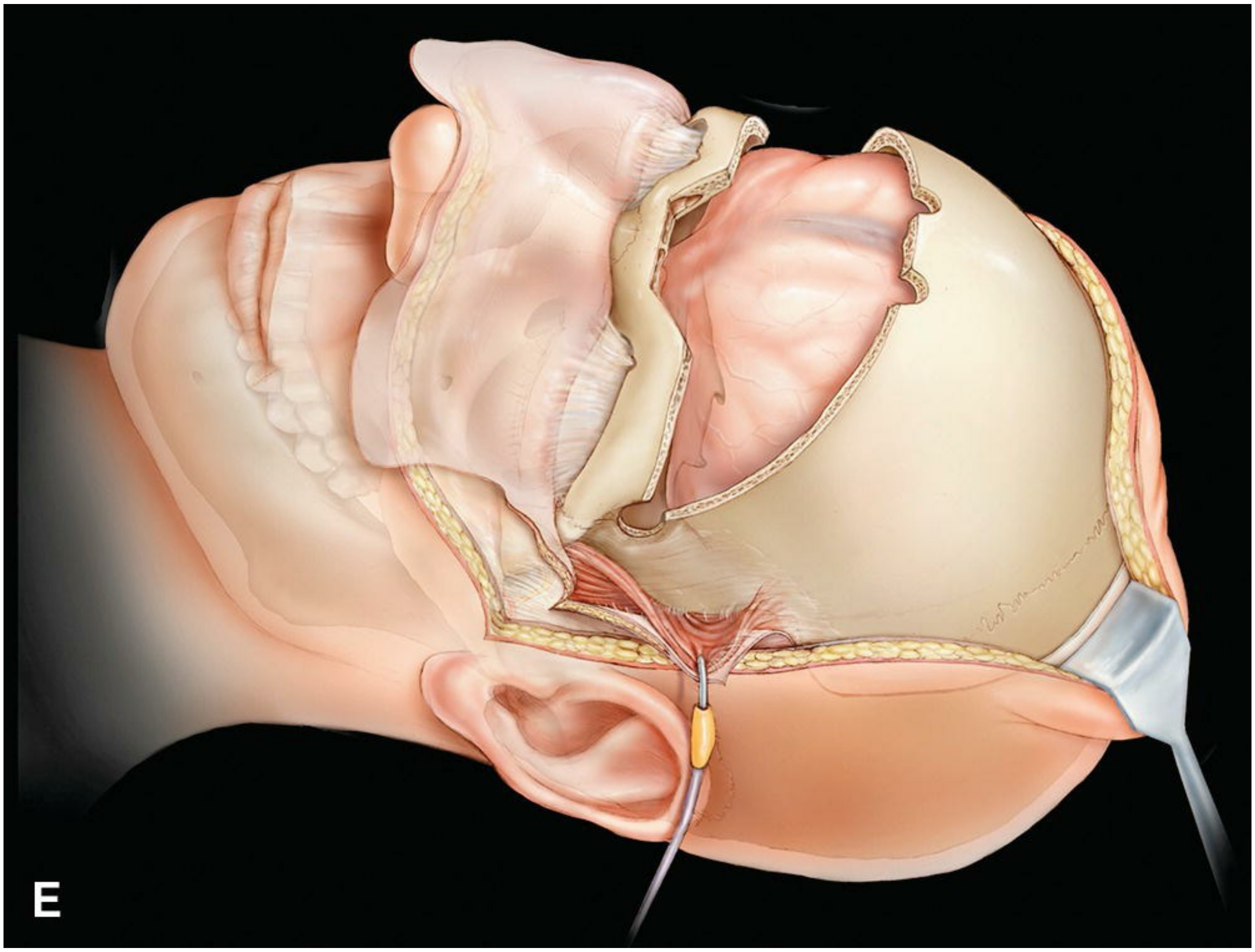
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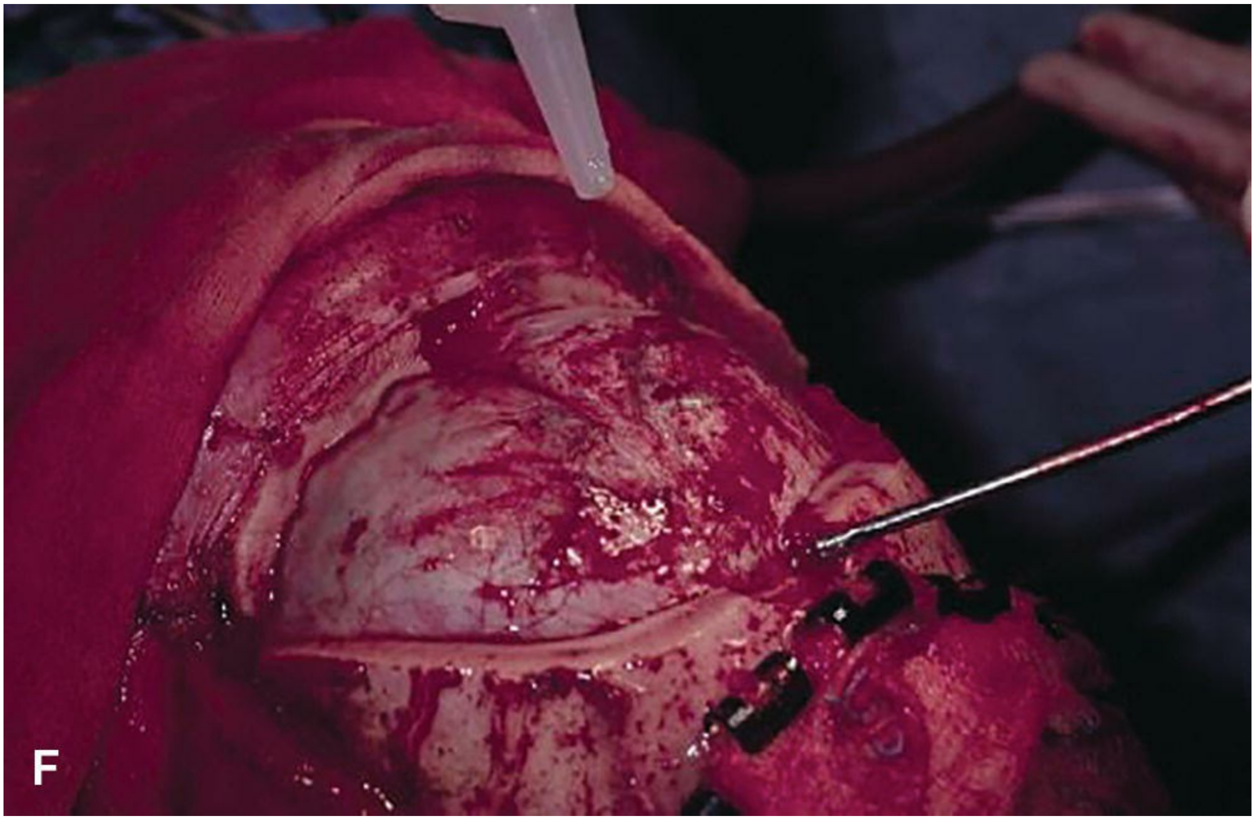


Figure 10.33. Frontal craniotomy. **A, B:** Bicoronal incision. **C:**Incision of the superficial layer of the deep temporalis fascia. Further dissection is done deep to this plane to preserve the frontal branch of the facial nerve. **D:** The pericranial flap. Adequate length and good vascular supply of the flap are prerequisites for effective reconstruction of the skull base defect. **E:**Frontal craniotomy (schematic). **F:** Frontal craniotomy (intraoperative photograph).

Pericranial incisions are made as far posteriorly as necessary to provide adequate length for the pericranial flap and along the superior temporal lines bilaterally. The pericranial flap is dissected free from the underlying bone and reflected anteriorly (**Fig. 10.33D**). Careful dissection and preservation of the supraorbital neurovascular pedicles are necessary in providing a well-vascularized pericranial flap for reconstruction of the cranial base defect. The supraorbital nerves and vessels are located along the medial one-third of the superior orbital rim. Elevation of the supraorbital rim periosteum begins laterally and proceeds medially, until the margin of the supraorbital groove is carefully exposed with a fine elevator. The nerve and vessels may exit the skull either through a notch or a true foramen. If a notch is present, then the nerve can be dissected free without difficulty. If a foramen rather than a notch

is found, the floor of the foramen is removed with a fine osteotome. This liberates the pedicle, and further elevation of the superior periorbita is then achieved. The periorbita is dissected free from both the superior and medial orbital walls bilaterally. The anterior ethmoidal vessels may by electrocoagulated by bipolar diathermy.

Frontal, temporal, or frontotemporal craniotomy is then performed to allow access to the floor of the anterior or middle cranial fossa or both, respectively. For a *frontal craniotomy*, bilateral burr holes are then placed in the depression posterior to the frontal-zygomatic sutures, after reflection of the temporalis muscle leaving a cuff of muscle at the superior temporal line for reattaching the muscle during closure (**Fig. 10.33E**). These anatomic keyholes provide access to the anterior fossa dura and periorbita, separated by the bony orbital roof. Burr holes are then placed on either side of the SSS, well anterior to the coronal suture. The bifrontal craniotomy is performed between the burr holes, with the burr holes straddling the SSS connected last. The dura of the anterior fossa is dissected from the orbital roofs. Under direct vision, orbital roof osteotomies are performed using a small osteotome.

Compared to frontal craniotomy, *subfrontal approaches* have the advantage of minimizing brain retraction by providing wider and more direct exposure of the floor of the anterior cranial fossa[44] (**Fig. 10.34**). This is especially helpful in more posteriorly located lesions such as those involving the planum sphenoidale, clivus, orbital apex, and optic chiasm (**Fig. 10.35**). The subfrontal approach is done by adding osteotomies that allow incorporation of the superior orbit and/or nasal bone to the craniotomy. These skeletal elements may be removed in several subunits or as a single bone flap (**Fig. 10.36**). Bilateral *nasal osteotomies* are done along the lower border of the nasal bones and then along the suture line between the nasal and lacrimal bones (Fig. 10.36C). The osteotomies are connected across the midline below the frontoethmoid suture line and in front of the anterior ethmoidal vessels. This avoids injury to the cribriform plate and olfactory nerves. After the dura and periorbita have been carefully dissected from the bone, the lateral wall and roof of each orbit are removed in separate *orbital osteotomies* (Fig. 10.36C). Under direct visualization, taking care to protect the periorbita and dura, an anteroposterior cut is made at the medial aspect of the orbital roof staying lateral to the ethmoid sinus. A second anteroposterior cut is made at the inferior aspect of the lateral orbital wall. These cuts are connected

posteriorly taking care to avoid the SOF. The bone flap consisting of the frontal bone, orbital roof, superior–lateral orbital rims, and nasal bones can be removed for wide exposure (Fig. 10.36D and E).

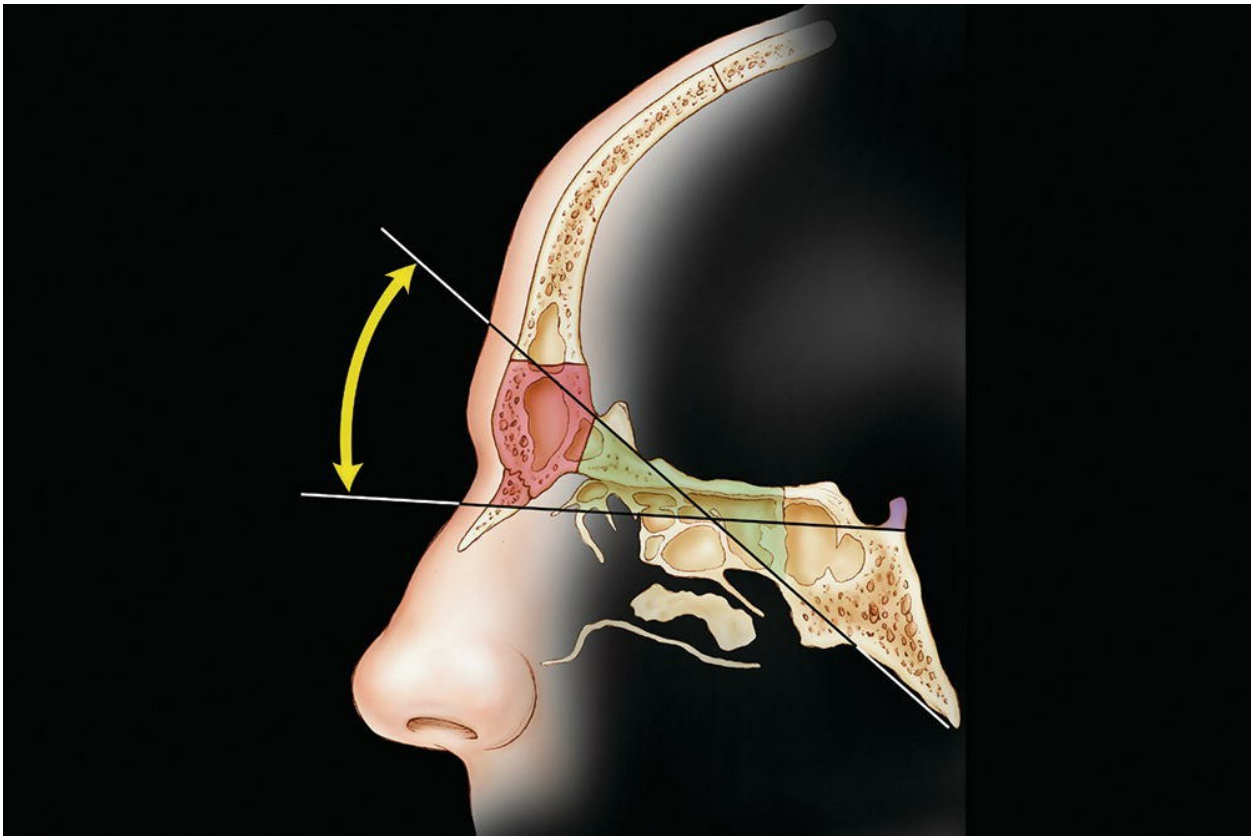
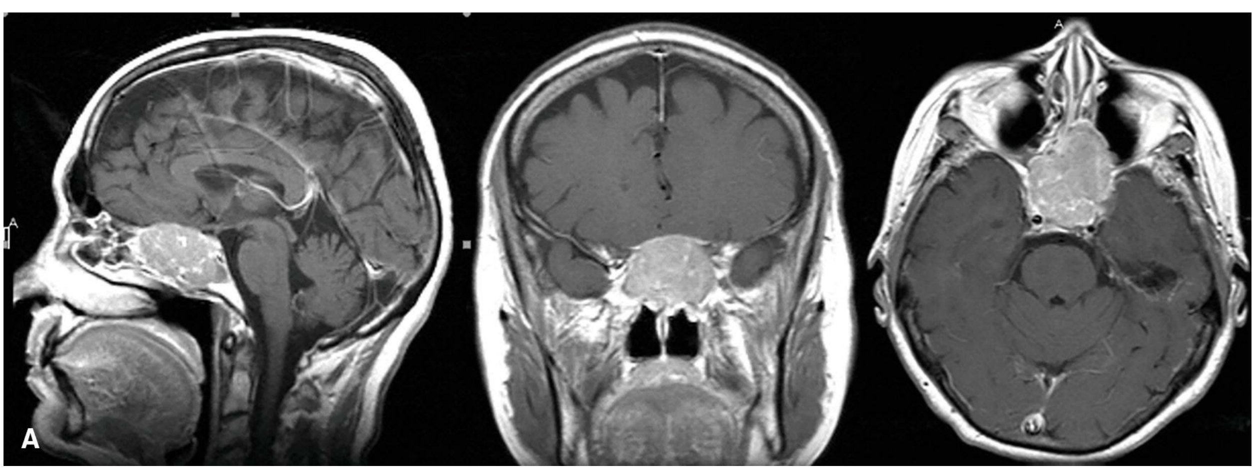


Figure 10.34. Subfrontal approach. Note the increased basal exposure provided by the subfrontal approach by incorporating the supraorbital rim, glabella, and nasal bone with the frontal craniotomy.



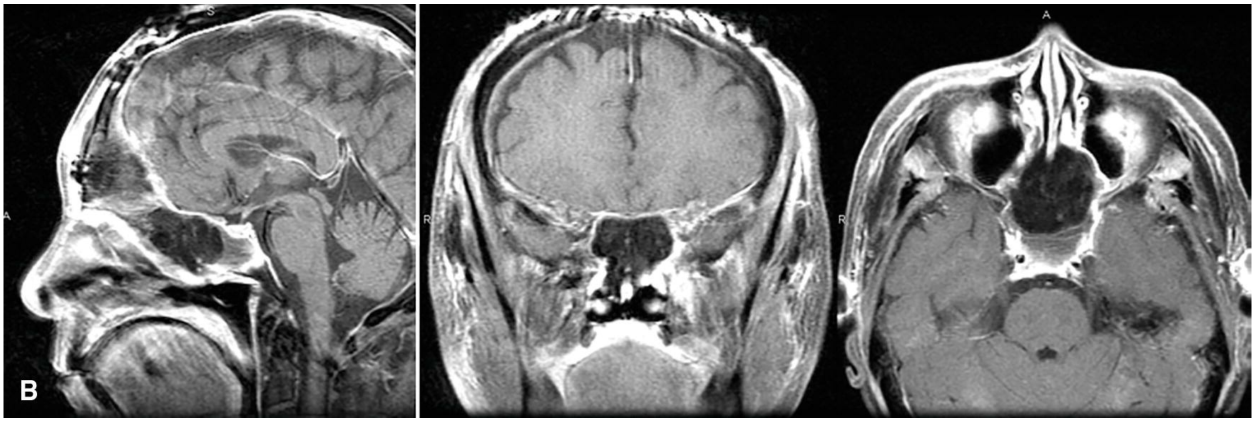
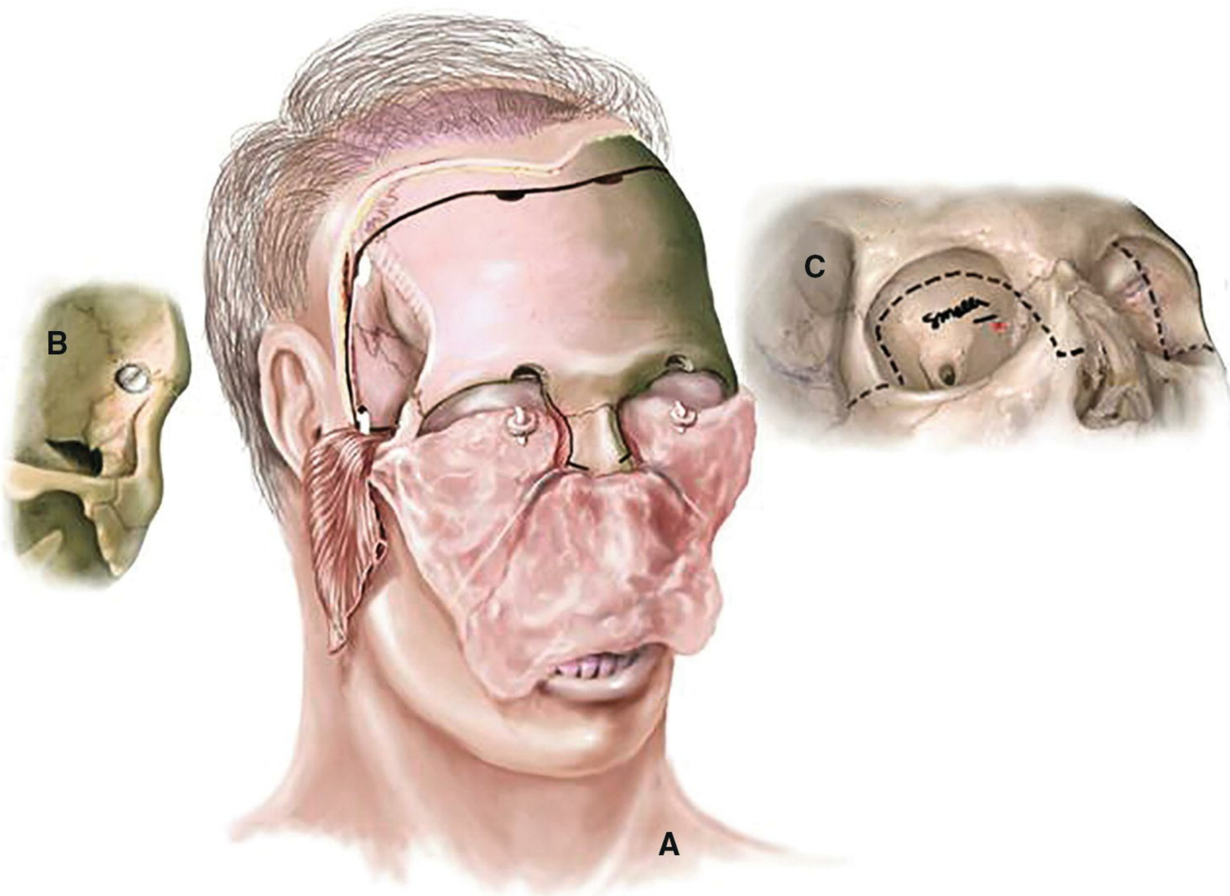
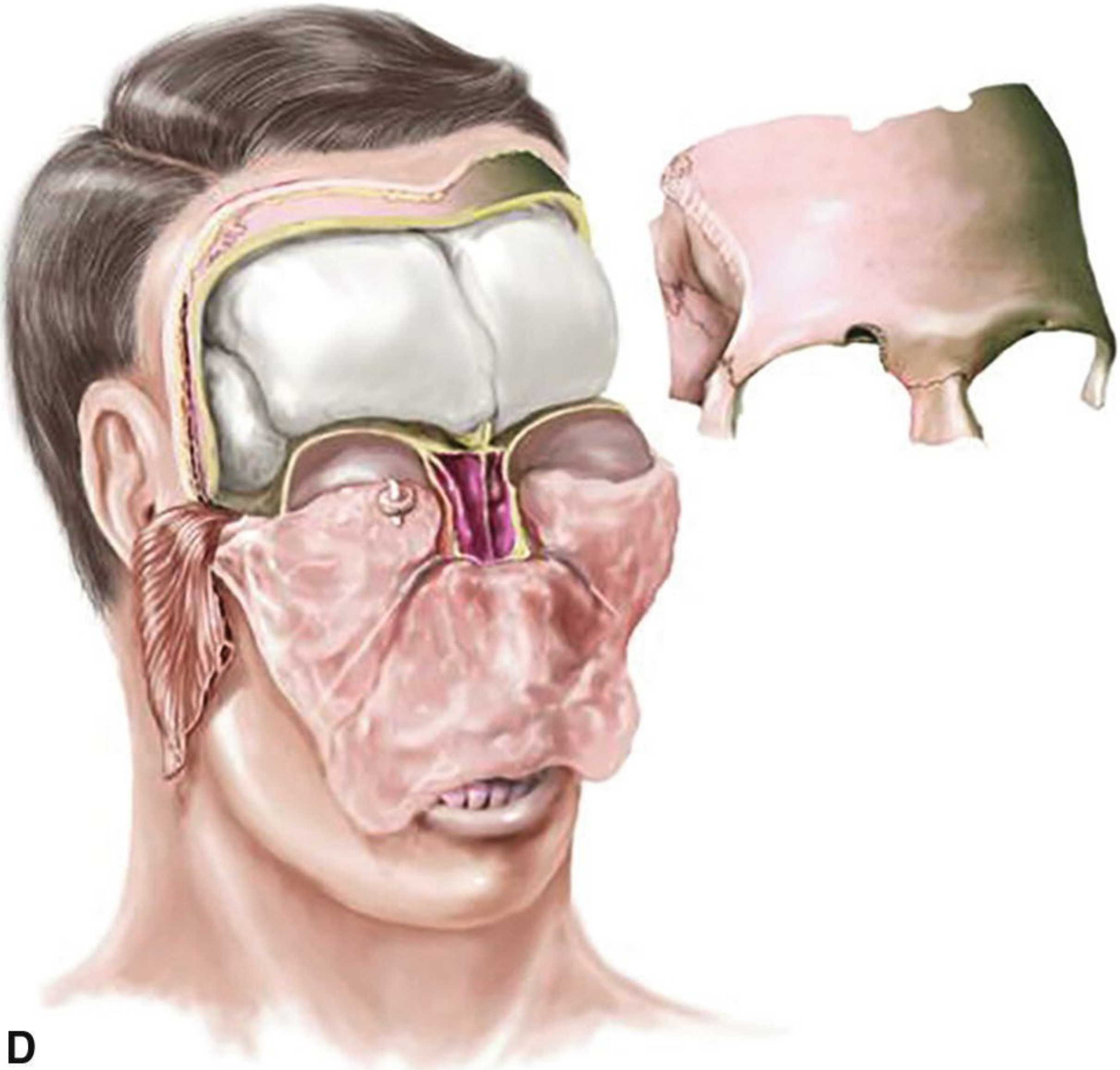


Figure 10.35. Pre- **(A)** and postoperative **(B)** MRI of tumor involving the planum sphenoidale and upper two-thirds of the clivus removed via a subfrontal approach.





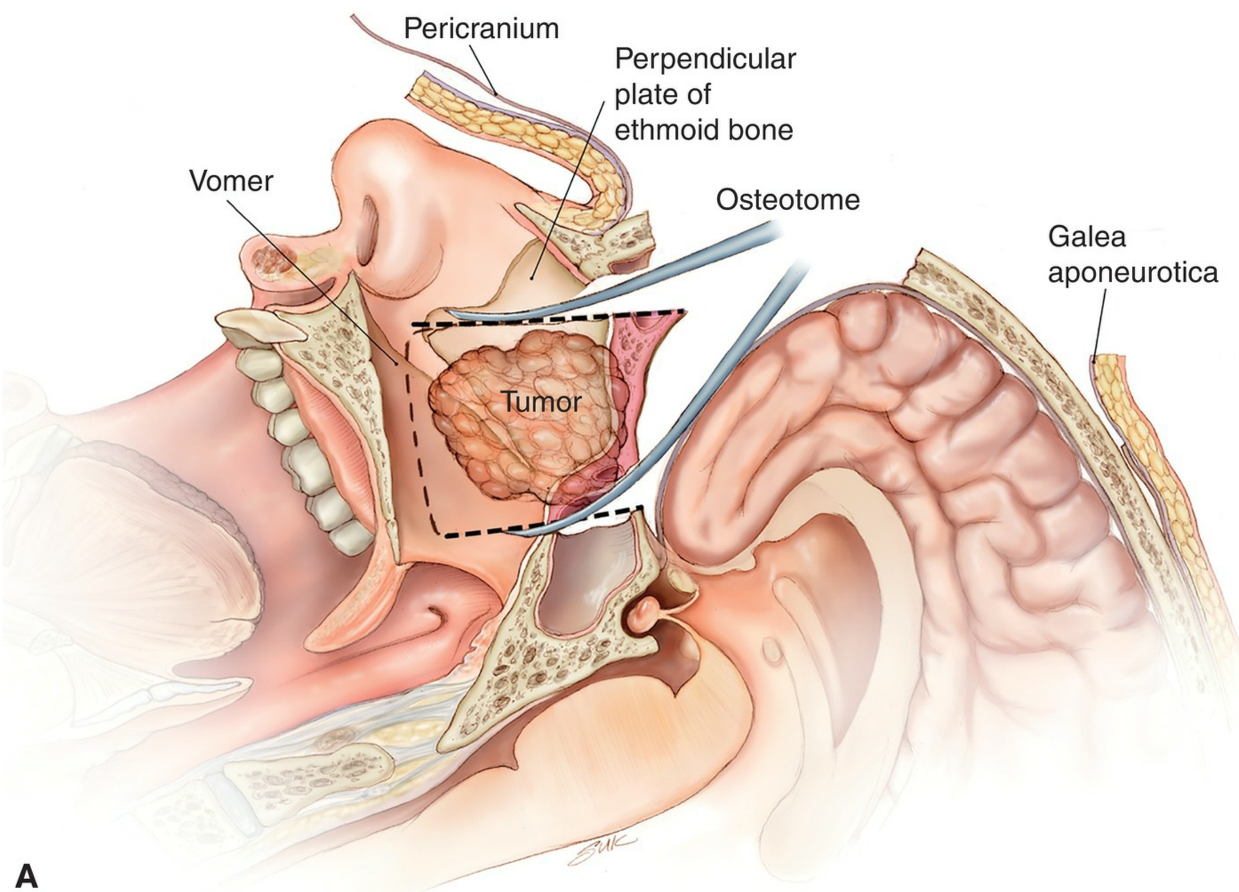
D

Figure 10.36. Subfrontal approach. **A:** Bicoronal incision and soft tissue dissection. The scalp flap is reflected anteriorly down to the level of the nasal bones. The supraorbital nerves were surrounded by complete foramina rather than a notch. Osteotomies around the foramina allow downward reflection of the nerves with the soft tissue flap. Burr holes are placed on either side of the SSS, anterior to the coronal suture. **B:** Bilateral burr holes are placed posterior to the frontal–zygomatic sutures. These anatomic keyholes provide access to the anterior fossa dura and periorbita, separated by the bony orbital roof. **C:** Orbital and nasal osteotomies. **D and E:** The cranio-orbital-nasal bone flap is removed as a single unit as illustrated by the diagram **(D)**, and intraoperative photograph **(E)**.

After completing the craniotomy, brain "relaxation" is achieved by withdrawing 25 to 50 mL of CSF from the lumbar subarachnoid drain, hypocapnia through controlled hyperventilation, mannitol diuresis, or steroids. This also lessens the need for brain retraction, which minimizes postoperative brain edema.[44] Next, the *dura* is carefully dissected along the floor of the anterior cranial fossa to expose the crista galli and olfactory grooves. The *olfactory nerves* are transected to expose the cribriform plate.

Dural elevation is continued to expose the fovea ethmoidalis and orbital roofs. Posteriorly, the planum sphenoidale and the base of the anterior clinoid process may be exposed as dictated by the extent of the tumor. If the dura is involved by the tumor, dura incisions are made around the tumor, and the dissection proceeds in a subdural plane, and the dura and even brain tissue if involved are resected along with the tumor.

With simultaneous exposure provided superiorly through the intracranial approach and inferiorly through the extracranial approach, osteotomies of the cranial floor around the tumor can be safely completed. Malleable retractors are used to protect the brain and the orbit as osteotomies are made. The placement of osteotomies and the extent of resection are dictated by the extent of tumor involvement and tailored in each case. Typically, however, osteotomies are made from the planum sphenoidale, along the roof of the ethmoid, and forward to the front of the cribriform plate (**Fig. 10.37**). Frozen section control of the margins should be done to ensure the adequacy of resection.



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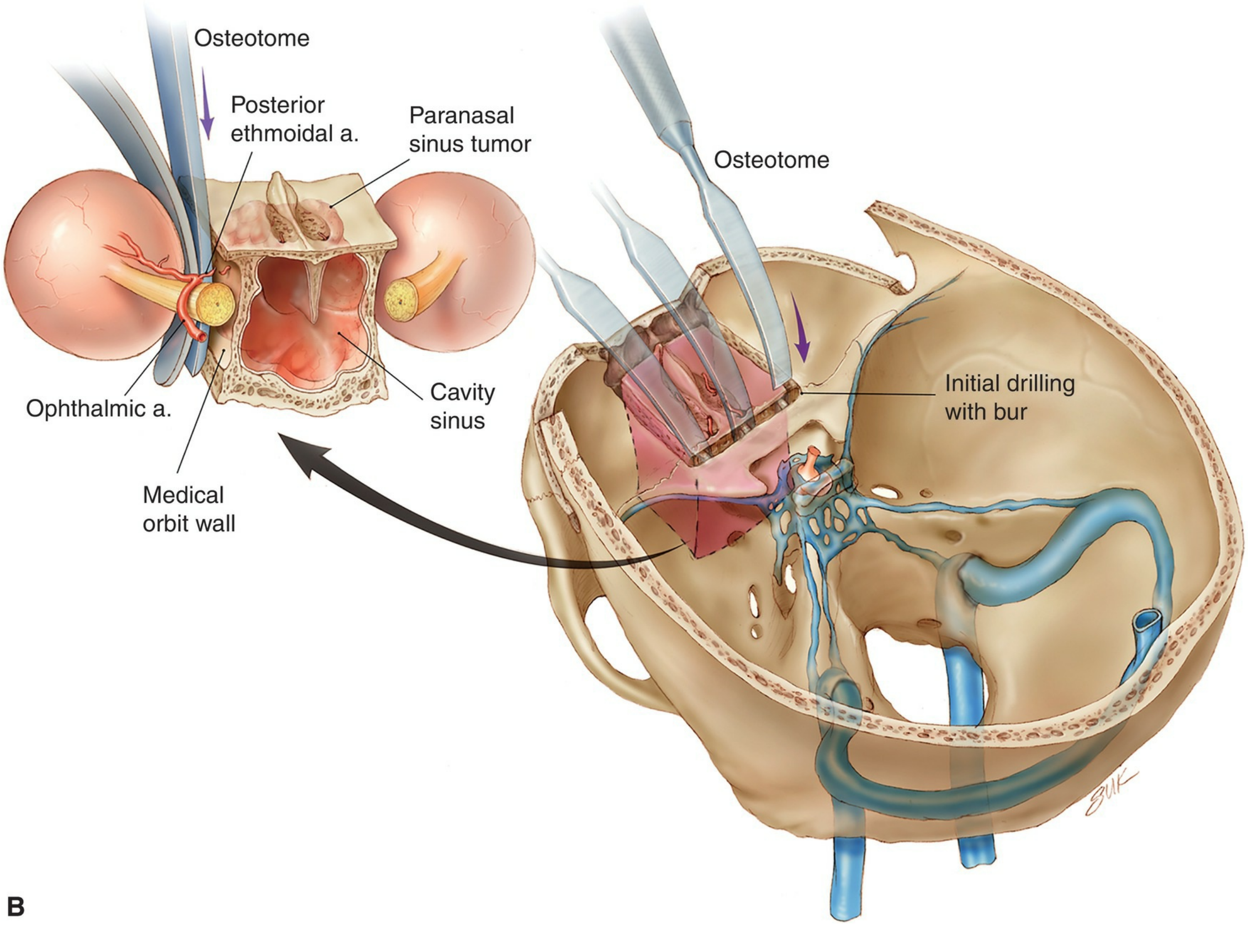
Osteotome
Posterior
ethmoidal a.
Paranasal
sinus tumor
Ophthalmic a.
Cavity
sinus
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orbit wall
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B

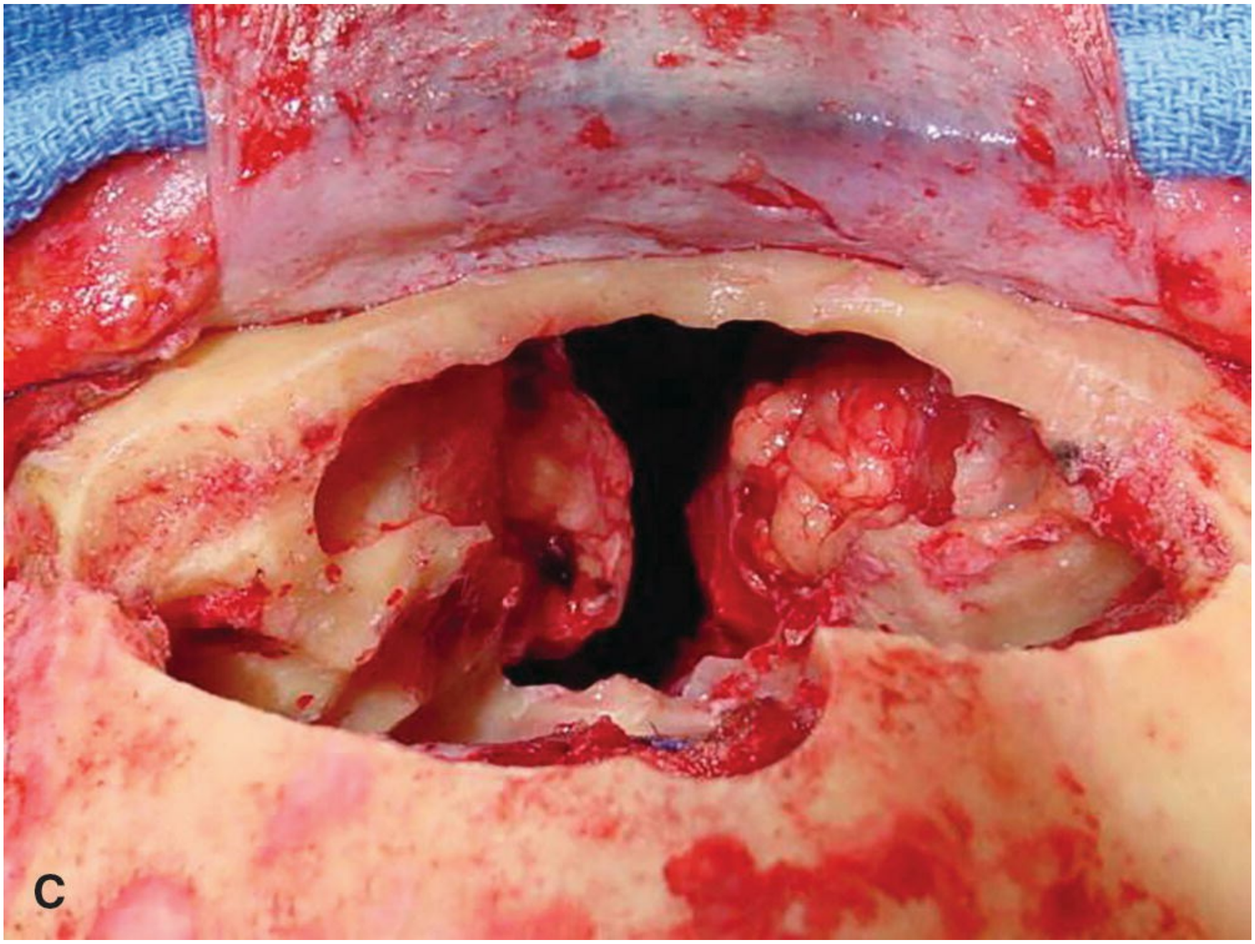

Figure 10.37. Resection of the floor of the anterior cranial fossa. **A and B:** Osteotomies along the floor of the anterior cranial fossa. **C:** Intraoperative photograph showing resection of the floor of the anterior cranial fossa and the medial orbital walls.

Management of the Orbit.

Every effort should be made to preserve the eye as long as preservation does not compromise the adequacy of oncologic resection. Attempts at orbital preservation in the face of gross residual disease however usually result in poor disease control and ultimate loss of orbital function. Most studies have shown that if orbital invasion is limited to the bony orbit or the periorbita, orbital preservation is possible without compromising oncologic outcome.[44,76] Orbital exenteration is usually indicated when there is gross invasion of the periocular fat, extraocular muscles, or optic nerve. The presence of proptosis or diplopia may be due to displacement rather than invasion of the intraorbital contents. Decreased visual acuity or visual fields,

or the presence of an afferent pupillary defect, usually indicates gross invasion of the orbit. Orbital invasion by perineural spread rather than direct extension may be missed unless careful examination of the cranial nerves especially V1 and V2 is done. Detailed neuro-ophthalmologic examination should be conducted on all patients with suspected or confirmed orbital involvement by sinonasal or other skull base tumors. If orbital exenteration is contemplated, always make sure that the patient has useful vision in the contralateral eye.

In the absence of any ocular signs or symptoms, however, evaluation of the extent of orbital involvement relies mainly on imaging. High-resolution CT and MRI are complimentary and provide critical information regarding the extent of orbital bony and soft tissue involvement, respectively. CT scans obtained at 1- to 3-mm slices with detailed bone windows are best for evaluating bony involvement of the orbital walls. MRI is best used to evaluate the extent of soft tissue invasion beyond the periorbita (**Fig. 10.38**). MRI is also useful in detecting perineural spread proximally beyond the orbital apex and into the CS or optic chiasm, which compromises surgical margins, local disease control, and survival and as such is a contraindication for surgical resection.[34] Even with the best imaging techniques, the definitive and most accurate assessment of the extent of orbital invasion and whether the eye could be preserved has to be made intraoperatively. This needs to be clearly discussed with the patient and family, and an informed consent for possible exenteration needs to be obtained in high-risk cases.

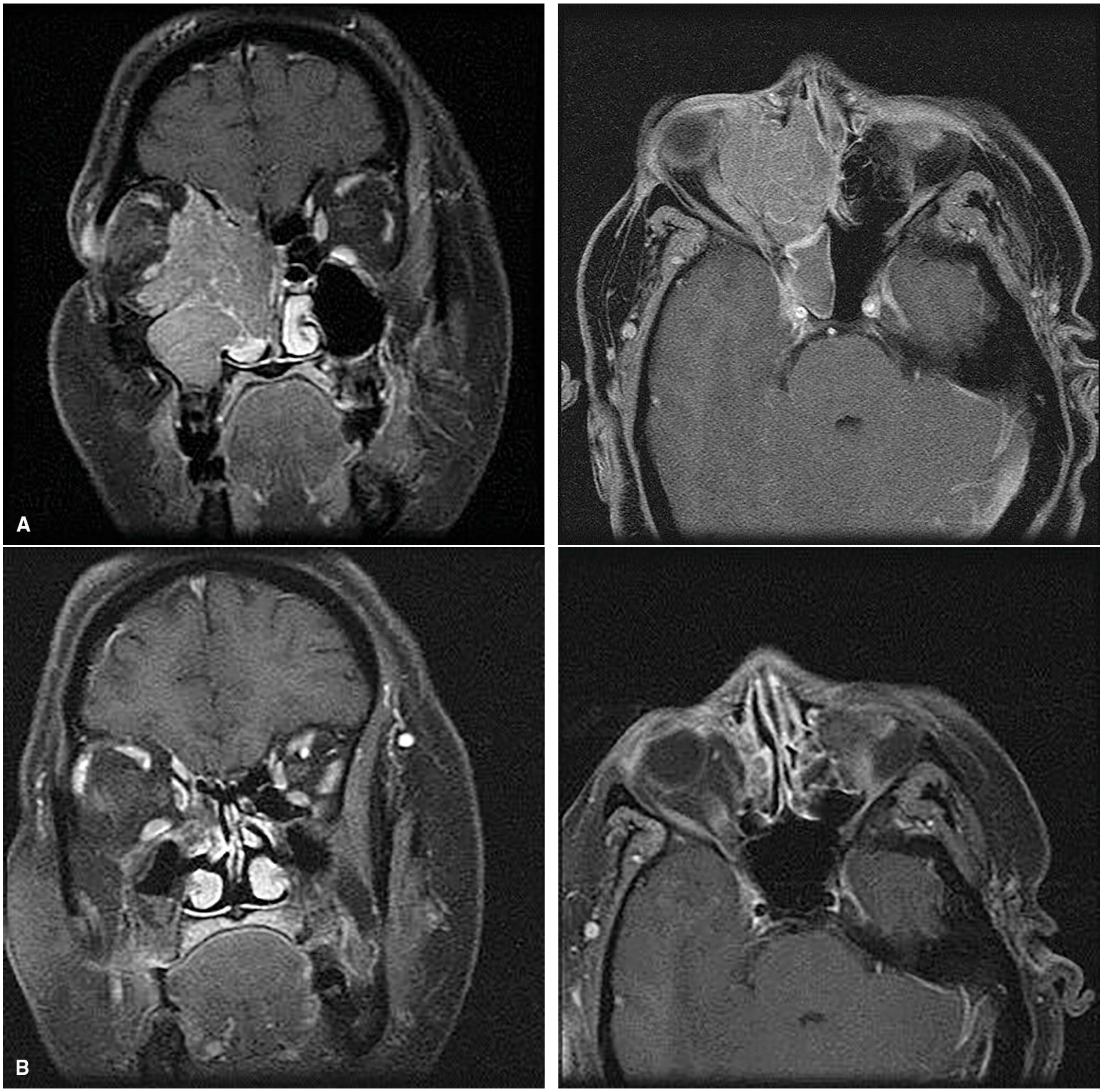

Figure 10.38. Sinonasal undifferentiated carcinoma with orbital invasion. **A:** MRI showing tumor of the right sinonasal region with gross invasion of the medial and inferior orbital contents. The tumor also invades the anterior skull base with limited intracranial extension. **B:** MRI of the same patient 3 years after completing treatment with induction chemotherapy followed by concurrent chemoradiation. Imaging shows no evidence of residual disease. Surgery was avoided, and the orbit was preserved.

There is an evolving role for induction chemotherapy and concurrent chemoradiation in the management of patients with orbital invasion by

advanced sinonasal cancers (Fig. 10.38). The role of such neoadjuvant treatment in enhancing the chances of orbital preservation continues to be investigated.[77] In a recent study, Hanna et al.[78] reported on the results of induction chemotherapy prior to local therapy in 46 patients with advanced SCC of the paranasal sinuses. Despite the relatively high number (37 of 46) of T4 tumors, with high prevalence of orbital (n = 31) and skull base (n = 14) invasion, orbital preservation was feasible in all but six patients, local recurrence rate was low, and local disease control was high.

If a decision is made to exenterate the orbit, supra- and subciliary incisions are made around the upper and lower eyelids, respectively. This allows for preservation of the eyelids, which can be used to line the orbit. If the eyelids are involved with cancer, they must be included in the resection (**Fig. 10.39**). The periorbita is incised over the superior and lateral orbital rims. Dissection continues along the roof of the orbit and lateral walls, until the SOF and the optic foramen are exposed. Lidocaine is injected around these structures to block any autonomic-induced cardiac arrhythmias. To prevent troublesome bleeding, the neurovascular structures in the SOF are slowly and carefully isolated, ligated or clipped, and transected. The optic nerve and the ophthalmic artery are then managed in a similar fashion. The extraocular muscles are transected at their origin in the orbital apex. The medial and inferior orbit may be left attached to the specimen if en bloc resection of the eye in patients with sinonasal cancer is indicated. Osteotomies are done as previously described for total maxillectomy, except that the orbital bony cuts are connected at the orbital apex, rather than the inferior orbital fissure.

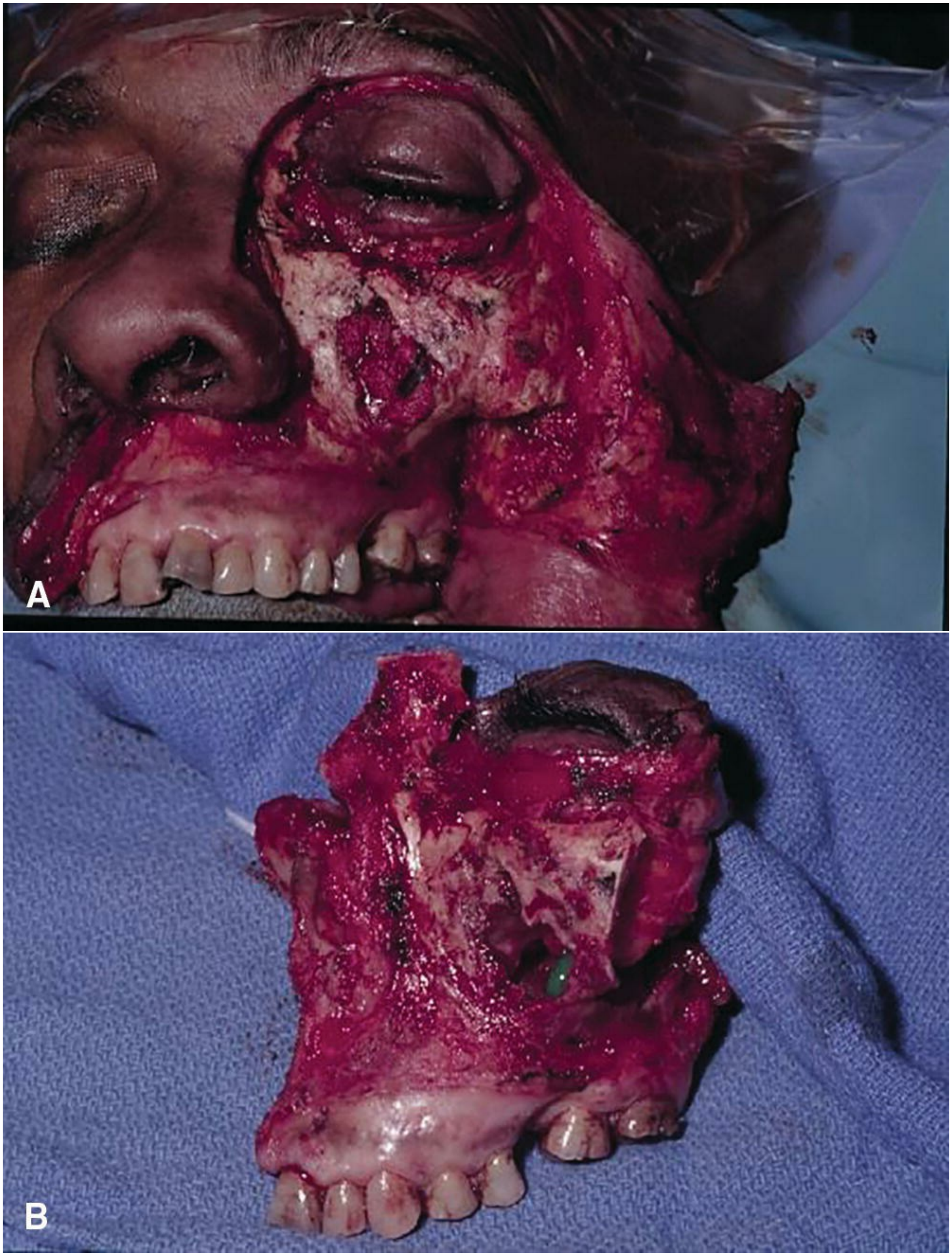
A
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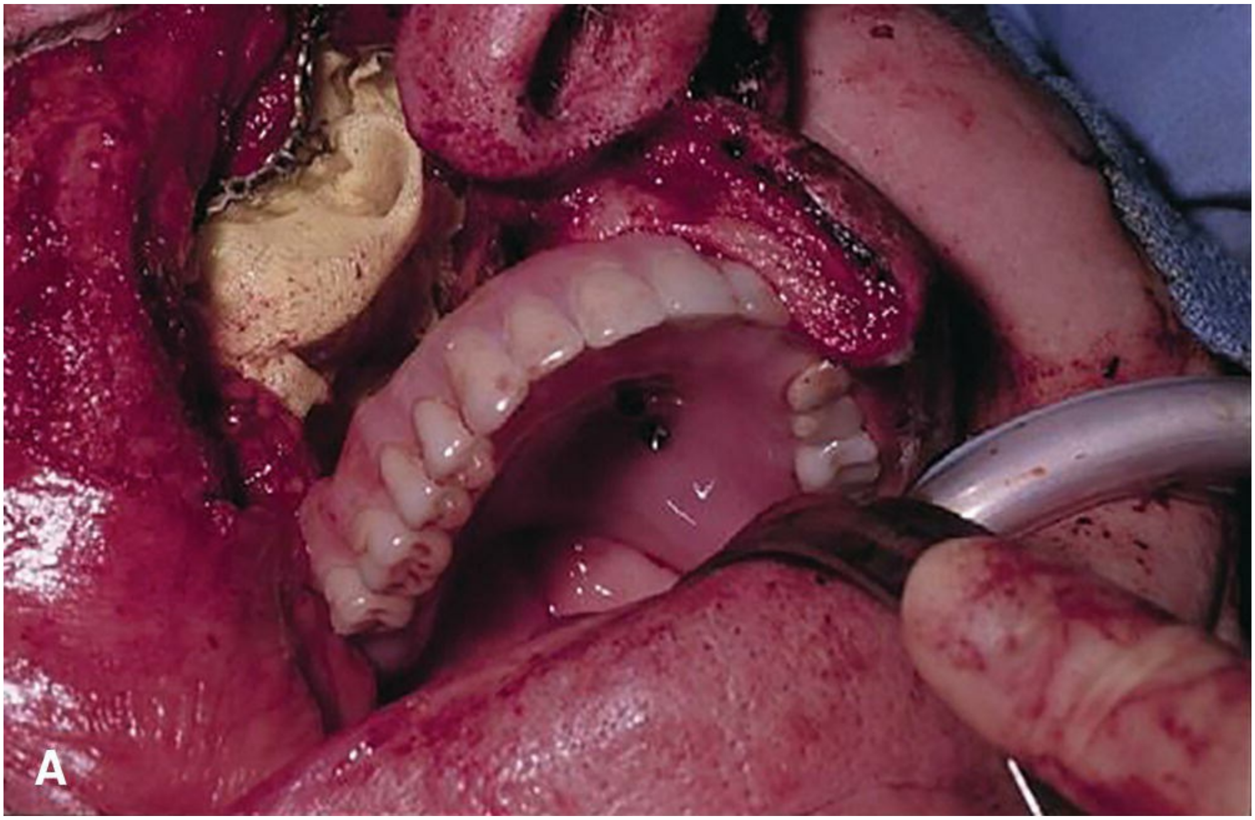
Figure 10.39. Orbital exenteration. **A:** Circumorbital incisions. **B:** Tumor specimen including en bloc resection of the maxilla and orbit. **C:** Immediate postoperative appearance.

Surgical Reconstruction

Oronasal Separation.

Effective separation between the oral and nasal cavities is essential for effective speech and deglutition. Palatal defects resulting from a maxillectomy are simply and effectively sealed using a prosthetic obturator. Preoperatively, the oromaxillofacial prosthodontist takes dental impressions and designs a *surgical* obturator, which is used at the end of surgery to seal the palatal defect (**Fig.** 10.40**A**). The surgical obturator can be slightly modified intraoperatively to custom-fit the defect. The advantages of this immediate reconstruction are early postoperative restoration of normal speech and oral feeding.[79] This minimizes the early postoperative morbidity of surgery and obviates the need for enteral feeding. Preoperatively, a clear communication between the head and neck surgeon and the maxillofacial prosthodontist concerning the anticipated maxillary defect is required for optimal results. An additional advantage of the surgical obturator is its ability to support the surgical packing used to immobilize the skin graft lining the cheek flap (Fig. 10.40A). This epithelial lining, when completely healed, minimizes granulation tissue formation, provides a smooth mucosal lining, reduces scar contracture of the cheek, provides a scar band to support the obturator, and facilitates cavity hygiene (**Fig. 10.41**). At the end of the first postoperative week, and after removal of the surgical packing, the surgical obturator is replaced with an *interim* obturator (Fig. 10.40B and C). This is used for several weeks after discharging the patient from the hospital and after completion of adjuvant therapy, allowing the surgical cavity to heal completely. Patients are instructed to remove the obturator periodically and clean the cavity with saline irrigation. At follow-up visits, the obturator is removed and cleaned of any crusts or debris. Finally, a *permanent* obturator is designed to custom-fit the cavity after it matures to its final shape and dimensions. The acrylic dome incorporated into its design provides some cheek support (Fig. 10.40D). In addition to being a simple and effective method of reconstruction of palatal defects, permanent obturators can also

provide full dental restoration (Fig. 10.40E). At follow-up visits, removal of the obturator allows for easy inspection of the cavity for any evidence of recurrent disease.



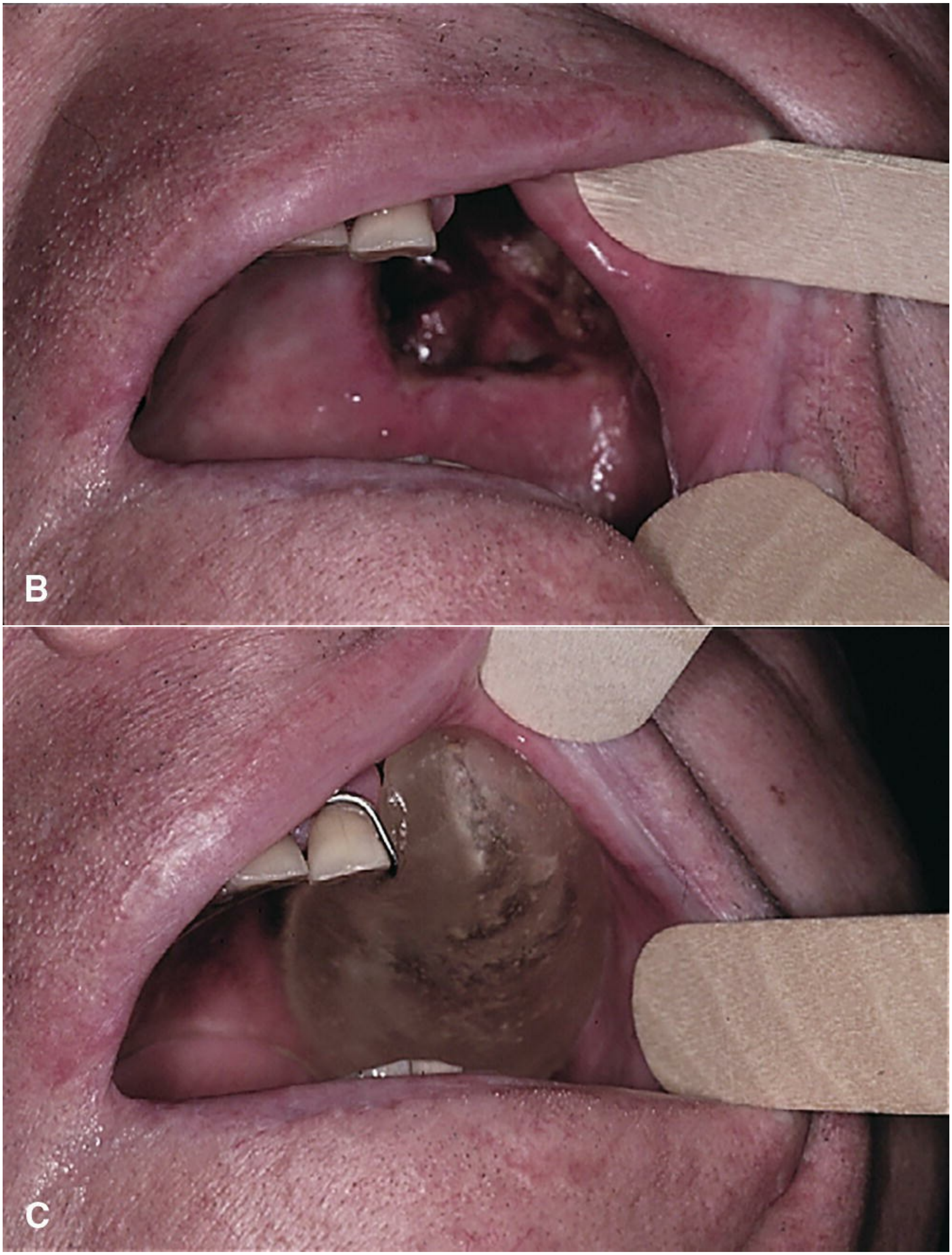
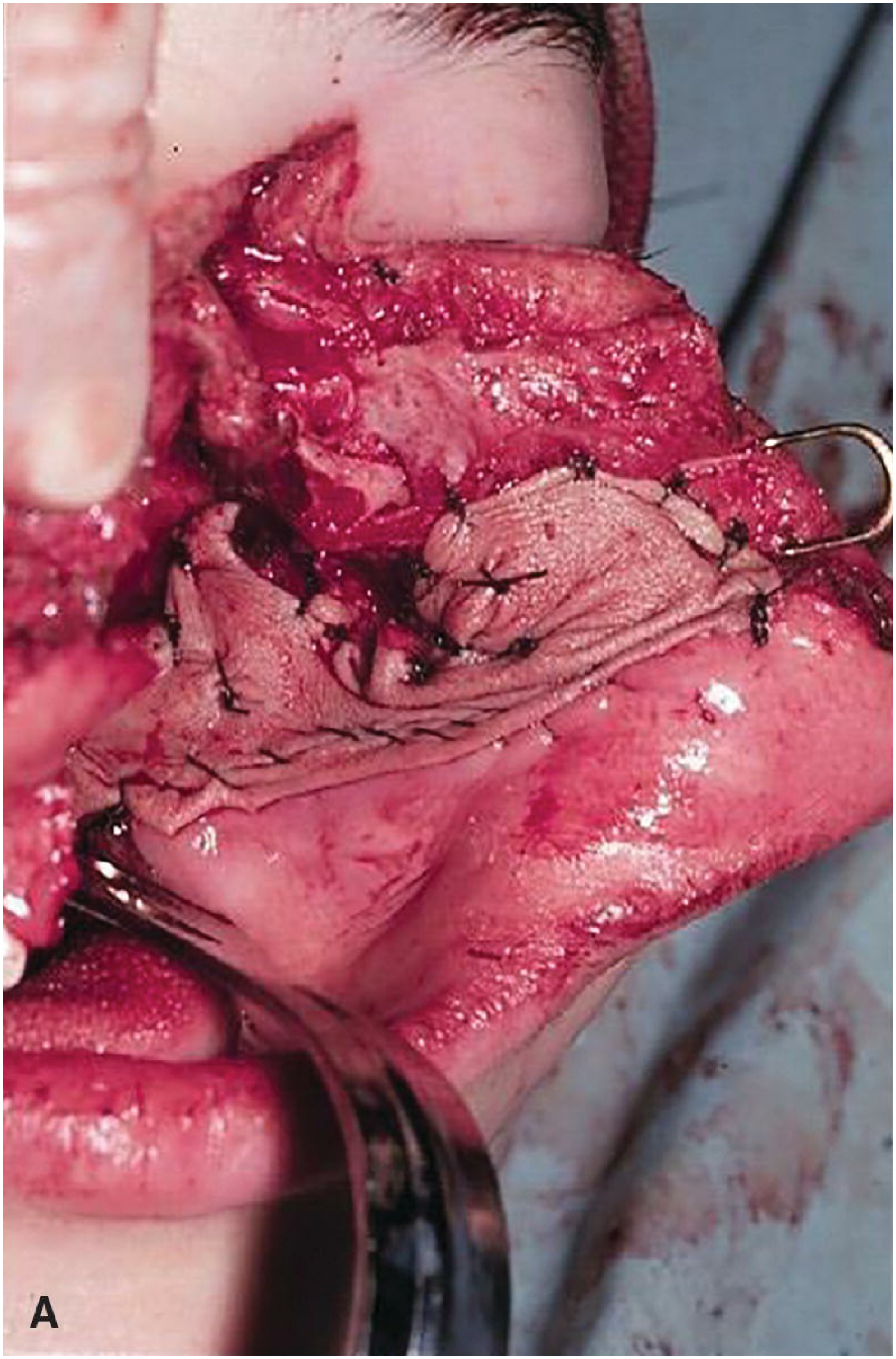

B
C

Figure 10.40. Prosthetic rehabilitation of postmaxillectomy palatal defect. **A:** Surgical obturator fixed to the palate with a lag screw providing immediate rehabilitation and supports the surgical packing. **B and C:** Interim obturator is used for several weeks until the cavity is completely healed. **D and E:** Permanent obturator has an acrylic dome to provide some cheek support. It also provides adequate dental restoration.



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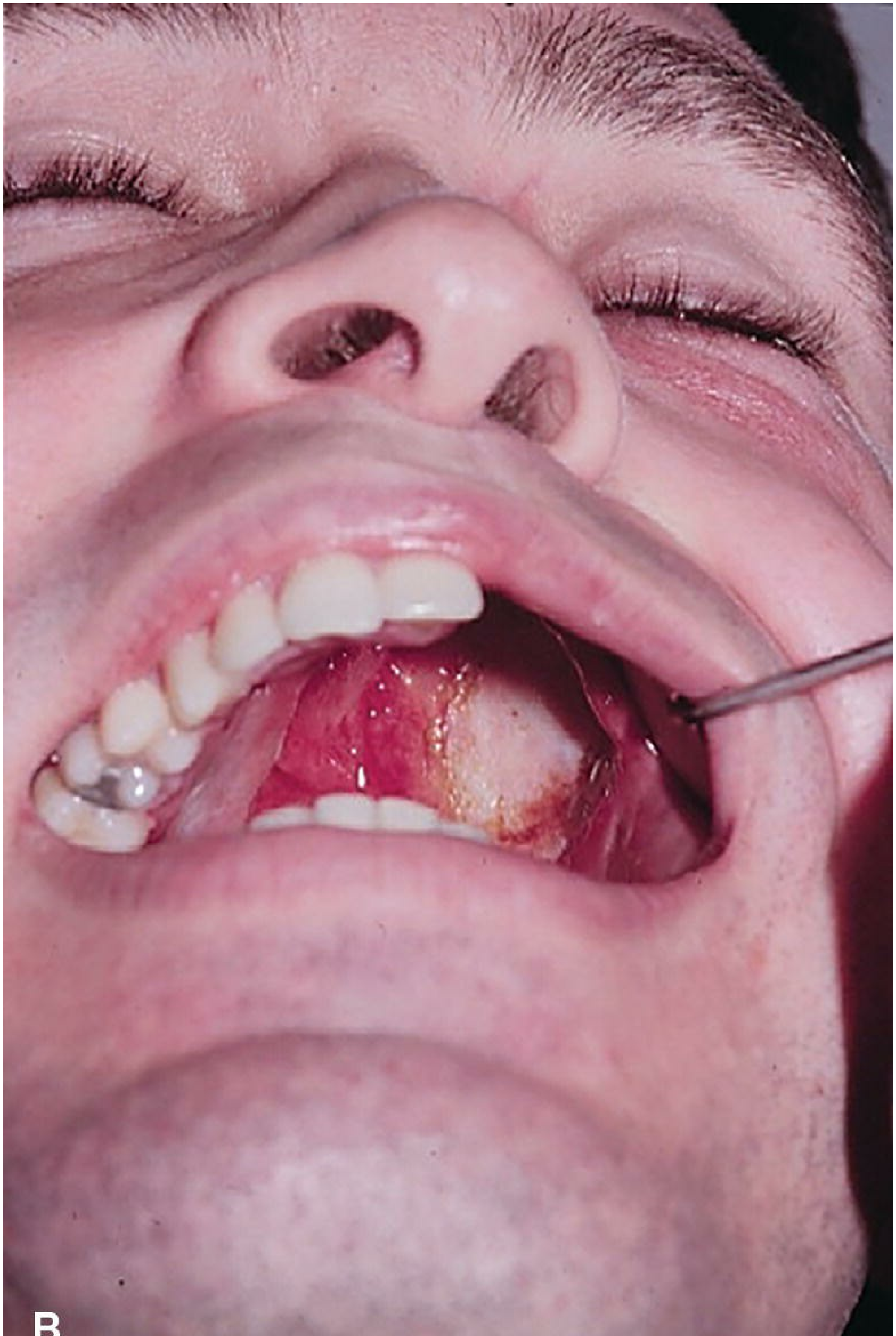


B

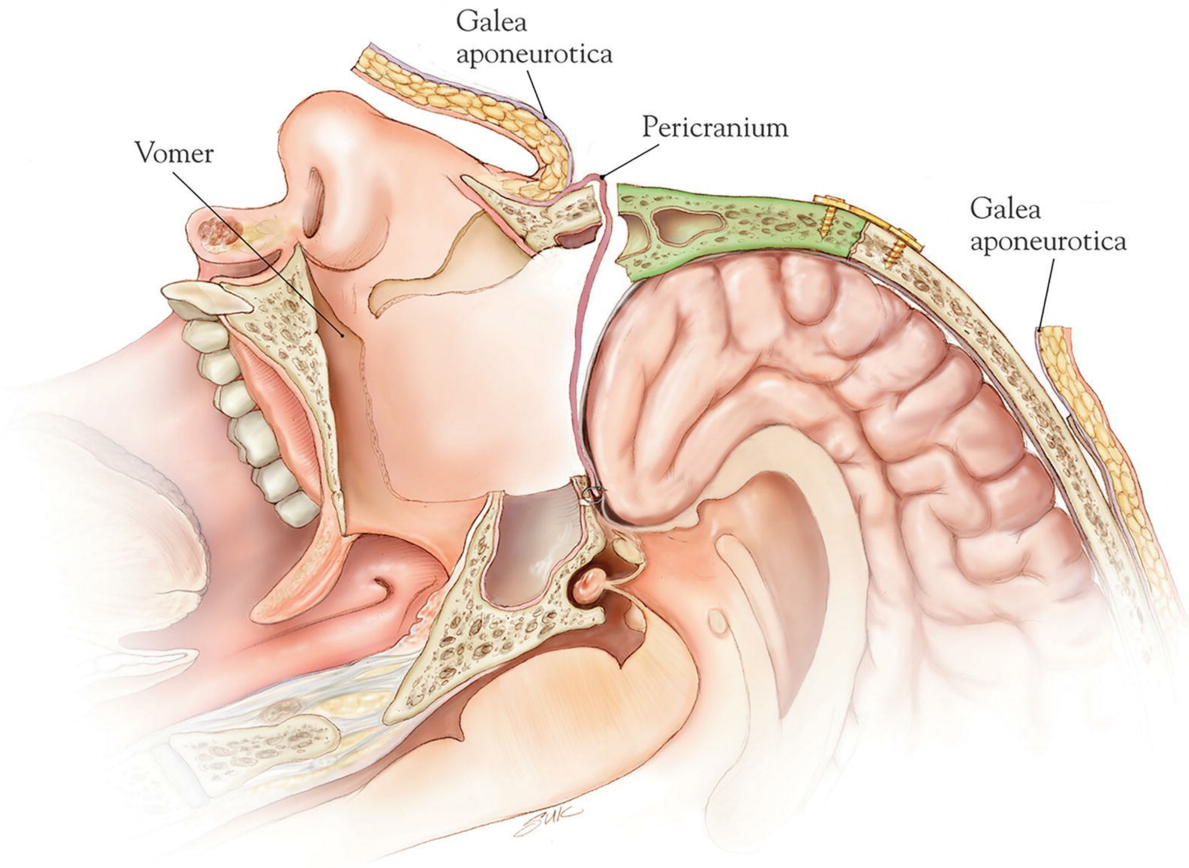
Figure 10.41. A STSG is used to line the surgical cavity and the deep aspect of the cheek flap **(A)**. Once healed, the STSG minimizes granulation tissue formation in the surgical cavity, prepares the surgical defect to receive an obturator, and reduces soft tissue contracture of the overlying cheek **(B)**.

Surgical reconstruction of palatal defects with tissue flaps has the advantage of eliminating the need for regular hygiene of the surgical cavity. Flap reconstruction however requires more extensive surgery, adds donor site morbidity, does not allow rapid dental restoration, and conceals the surgical cavity from inspection for recurrent tumor. These disadvantages make prosthetic obturators the method of choice for reconstruction of surgical defects of the palate. The use of tissue flaps is usually reserved to patients who need additional reconstruction to the maxillary skeleton, orbital floor, or cranial base. In a recent study from MDACC, analysis of the functional outcomes of 113 patients undergoing maxillectomy for cancer was performed.[79] Seventy-three patients received an obturator, and 40 patients were reconstructed with a free flap. They concluded that moderate-sized maxillectomy defects involving the palate can be successfully treated with either an obturator or free flap reconstruction. Extensive defects (more than 50% of the palate) have a better functional outcome (speech intelligibility and postoperative diet) with free flaps. Evidence does not suggest that free flap reconstructions delay diagnosis of local recurrences.

Cranionasal Separation.

Whenever the cranial and nasal cavities are joined by a surgical defect, as is the case with anterior craniofacial resection, watertight cranionasal separation is mandatory to reduce the risk of CSF leak, meningitis, and pneumocephalus. Meticulous closure of all dural tears should be done. Larger defects of the dura should be repaired using temporalis fascia, pericranium, or fascia lata grafts. Although bony reconstruction of the anterior skull base has been described using vascularized and nonvascularized bone grafts as well as bone cement, reconstruction of the bone defect is not routinely necessary in most patients.[44] The vascularized galeal–pericranial flap is currently the most frequently used flap for reconstructing defects of the floor of the anterior cranial fossa (Figs. 10.33D and **10.42**). Flap handling and suturing should be meticulous in order to achieve a watertight seal. Fibrin glue and tissue adhesives do not compensate for an imperfect closure. Lumbar subarachnoid

drainage for several days postoperatively helps to reduce CSF pressure and the possibility of a leak. However, aggressive lumbar drainage should be avoided because it may encourage the development of pneumocephalus.



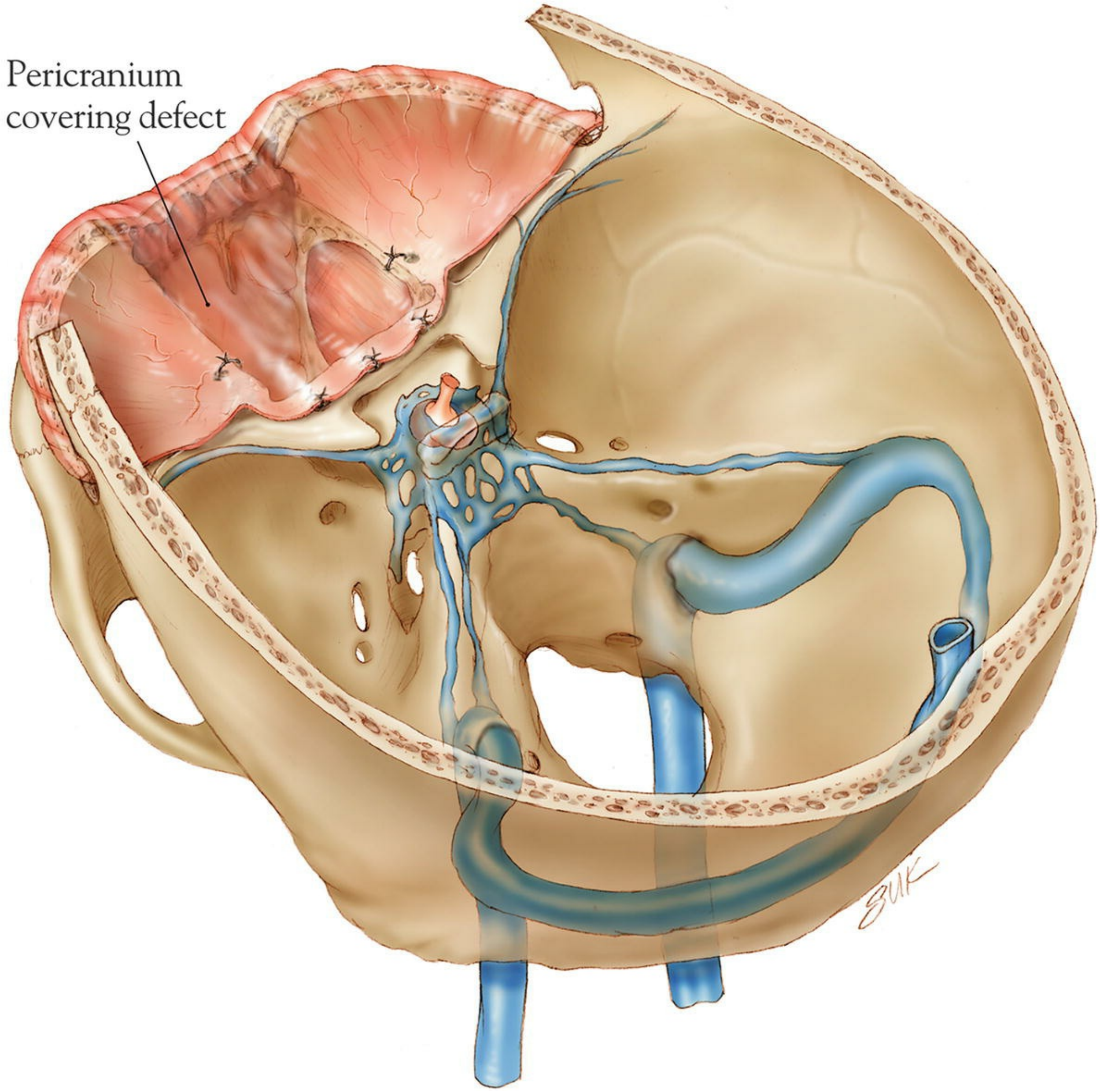


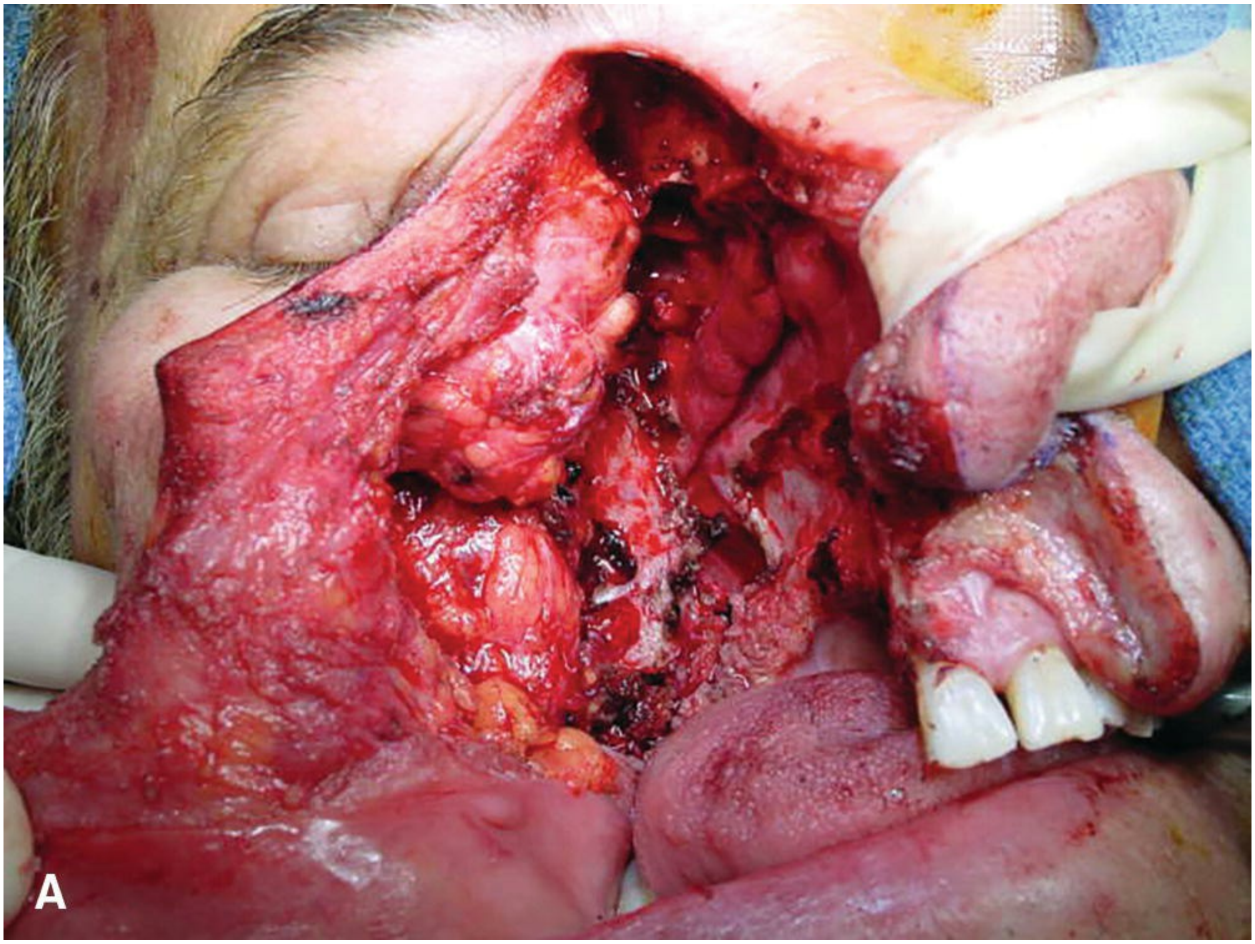
Figure 10.42. Schematic showing reconstruction of the floor of the anterior cranial base with pericranial flap.

Occasionally, more bulk is needed to reconstruct the surgical cavity and reduce dead space, such as with extensive defects of the cranial base. Regional flaps, such as the temporalis muscle, are usually adequate for this purpose. If the muscle bulk is inadequate, or if its blood supply has been sacrificed, then a microvascular free flap is used. Vascularized tissue may also be needed to protect the carotid artery if it is exposed to the surgical defect. This is done to prevent desiccation of the arterial wall and carotid

artery blowout. This is particularly important if the patient received prior radiation therapy or will receive postoperative adjuvant radiation.[48]

Orbital Reconstruction and Cheek Support.

The maxilla has three bony buttresses, the nasomaxillary, zygomaticomaxillary, and pterygomaxillary. In addition to a palatal defect, total maxillectomy results in resection of all three buttresses and loss of adequate skeletal support to the soft tissues of the cheek. Loss of the zygomaticomaxillary buttress results in inferior displacement of the orbit and flattening of the malar eminence. Loss of the nasomaxillary buttress results in superior and posterior deviation of the alar base of the nose. Loss of the pterygomaxillary buttress results in superior and posterior deviation of the upper lip. Resection of the inferior orbital rim and floor leads to loss of skeletal supports to the eyelid and globe. Lack of adequate orbital support results in unacceptable esthetic and functional outcome of the preserved eye due to enophthalmos, ectropion, hypoglobus, and diplopia. The combined effects of loss of support of the eye and cheek result in the “typical” postmaxillary deformity (**Fig.** 10.43**A and B**). Although a split thickness skin graft (STSG) and a palatal obturator are commonly used in reconstruction after maxillectomy, these methods of reconstruction do not provide adequate support for the cheek and eye.[79] In such cases, bony reconstruction is needed to provide adequate support for the cheek and eye and enhance postoperative appearance and function.




B

Figure 10.43. Orbital reconstruction. **A:** Post total maxillectomy surgical defect showing total loss of the orbital floor and periorbita. **B:** Without bony reconstruction, the result is “typical” postmaxillectomy deformity due to lack of support of the orbit and cheek. There is downward displacement of the orbit and medial canthus. Note the presence of enophthalmos as evidenced by a prominent upper eyelid sulcus. There is flattening of the cheek and deviation of the nasal tip. The patient had significant diplopia. These deformities can be avoided with adequate bony reconstruction. **C:** Postoperative appearance showing good position of the eye, cheek, and nose in a patient with bony reconstruction of the orbital floor and cheek.

The function of the preserved orbit will be greatly enhanced by meticulous orbital reconstruction.[80] Careful reattachment of the medial canthal ligament will prevent telecanthus. If the lacrimal apparatus is transected, marsupialization of the lacrimal sac into the surgical cavity or a dacryocystorhinostomy should be performed to avoid postoperative epiphora.

If the orbital rim or a significant portion (more than one-third) of the orbital floor is removed particularly if the periorbita is resected, then bony support is needed to prevent enophthalmos, ectropion, hypoglobus, and diplopia. Bone reconstruction is best done using vascularized bone flaps. If nonvascularized bone grafts or alloplastic implants (e.g., titanium mesh) are used, then they should be adequately covered with well-vascularized soft tissue to minimize resorption of bone grafts and infection and extrusion of alloplastic implants (**Fig. 10.43A and C**).

The pedicled temporalis muscle flap, temporoparietal fascial flap, or septal mucosal flap are most commonly used for this purpose. Microvascular free flaps may be used to either provide soft tissue coverage of bone grafts or implants, or composite vascularized bone flaps may be used for full reconstruction of both soft tissue and bone defects.[48]

Primary reconstruction of defects of the maxilla and orbit at the time of maxillectomy is easier and results in better esthetic and functional outcome than delayed reconstruction. Although secondary reconstruction after globe-sparing maxillectomy is feasible, it is often difficult and the results are limited by excessive scarring and soft tissue contracture, especially in patients who underwent adjuvant radiation therapy. These patients may benefit more from free-tissue transfer reconstruction.[48]

The function of the preserved eye will also be greatly influenced by precise dosimetry of postoperative radiation. The use of IMRT and more recently proton therapy is particularly helpful in delivering effective radiation doses to the tumor bed while sparing ocular contents. In a report from MDACC, the use of IMRT improved the dose distributions within the target volume, reducing the late grade 3 to 4 complication rates (particularly ocular) from 34% to 8% ($p = 0.014$).[37]

Dental Restoration.

Prosthetic rehabilitation using partial or full upper dentures is the easiest method of dental restoration in patients who have undergone maxillectomy (Fig. 10.40). Remaining contralateral teeth facilitate retention of partial dentures. In edentulous patients, dental fixatives can be used, but denture retention is more difficult. A soft palate “band” at the posterior edge of the defect may provide enough of a ledge for retaining the prosthesis. Retention of the prosthesis in edentulous patients who underwent an extended resection

to include the soft palate may be extremely difficult. In such cases, the use of osseointegrated implants facilitates prosthetic dental restoration.[79]

Another important aspect in the rehabilitation of patients after maxillectomy is the prevention of trismus. Patients who have undergone resection of the pterygoid plates or muscles of mastication are particularly prone to develop trismus. This may be severe enough to interfere with inserting and wearing a denture-bearing obturator. Early postoperative jaw opening exercises using "stacked" wooden tongue blades, or commercially available devices (e.g., Therabite), are extremely important in preventing or minimizing postoperative trismus (**Fig. 10.44**).


A

Figure 10.44. A and B: This 15-year-old boy underwent a resection of a nasopharyngeal angiofibroma, which involved the pterygoid plates. Postoperatively, he had significant trismus, which resolved with mouth-opening exercises.

Restoration of Facial Defects.

Smaller defects of the face are optimally reconstructed using local flaps. Local skin flaps provide the best thickness and color match for facial defects. Reconstruction of more extensive facial defects may require regional or microvascular free flaps, but suffer from less optimal esthetic outcome due to color or thickness mismatch between the donor and defect sites (**Fig. 10.45**). Facial defects resulting from orbital exenteration or total rhinectomy are best managed with prosthetic restoration[48,81] (**Fig. 10.46**).


A


B

Figure 10.45. A: Maxillary sinus cancer involving the overlying cheek skin. **B:** Maxillectomy and facial defect. **C:** Reconstruction with a rectus abdominis free flap. Note the color and thickness mismatch.

Figure 10.46. A: Orbital exenteration defect. **B:** Prosthetic rehabilitation.

Cervical Metastasis.

The incidence of lymph nodal metastasis at presentation ranges from 3% to 26%, and several authors have reported high rates of neck recurrences in untreated necks that can reach up to 30%.[82,83] Although the most frequently reported sites of lymphatic metastasis are level I and II, a significant part of the lymphatic drainage of the paranasal sinuses and the nasal cavity is directed to the retropharyngeal lymph nodes, which are inaccessible for palpation and are frequently overlooked. It is possible, therefore, that the true incidence of lymphatic spread of sinonasal malignancy is underestimated. The retropharyngeal lymph nodes are best evaluated with high-resolution imaging (CT or MRI) or PET–CT.

The overall risk of nodal involvement at either diagnosis or as regional recurrence may depend on the histology and the stage and extent of the primary tumor. High-grade tumors such as SCC and SNUC and advanced stage (T3 to T4) tumors have a relatively higher rate of nodal involvement.[37] Tumor extension into the oral cavity and nasopharynx is also associated with increased risk of nodal metastasis.[82,83]

Lymphatic metastasis to the cervical lymph nodes carries with it a poor prognosis in patients with cancer of the SNT. In a study of 146 patients with maxillary sinus cancer treated at MDACC,[37] patients presenting with node-negative versus node-positive disease had an estimated 5-year OS rate of 56% versus 44%, respectively ($p = 0.06$) (**Fig. 10.47**).

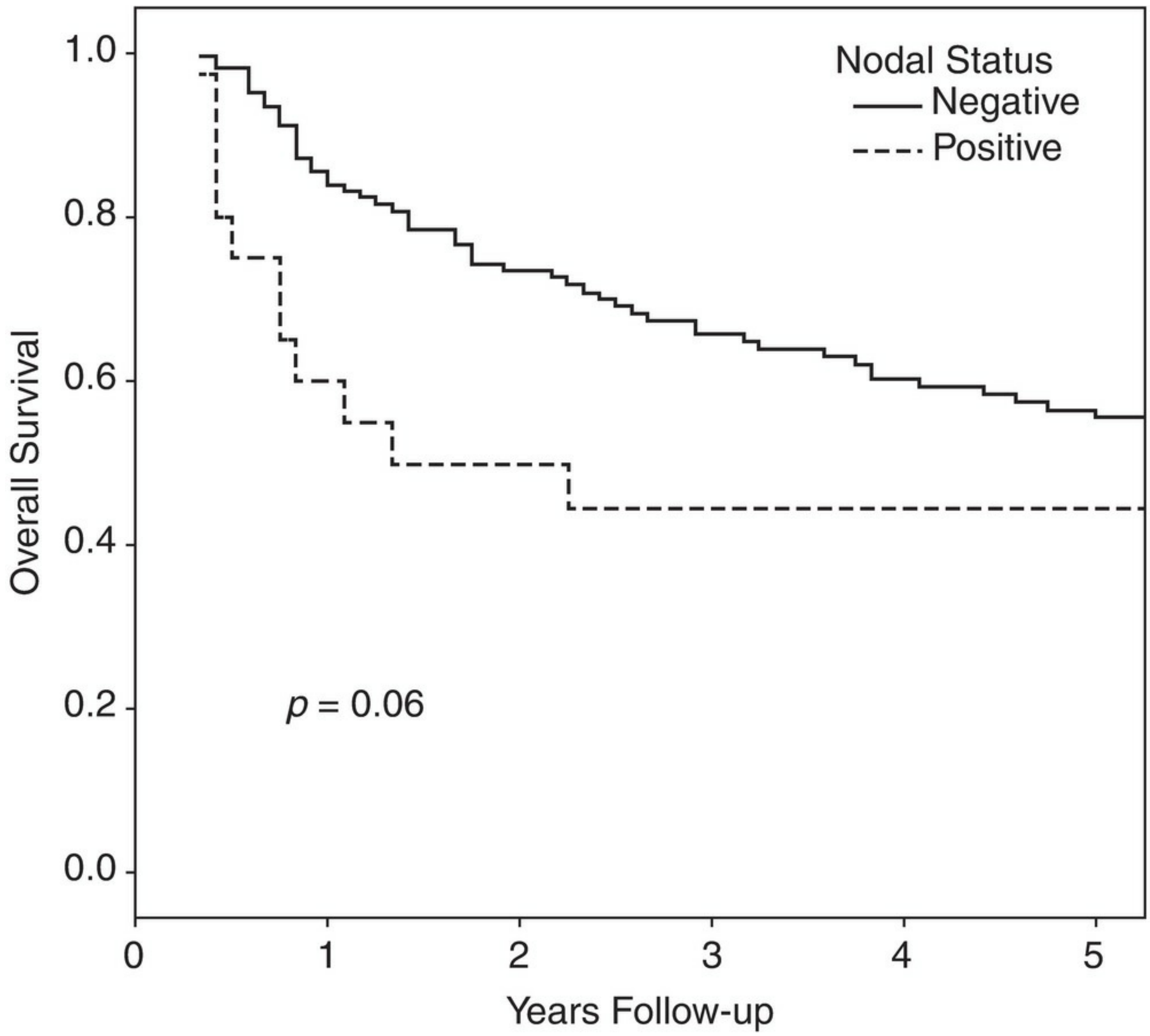
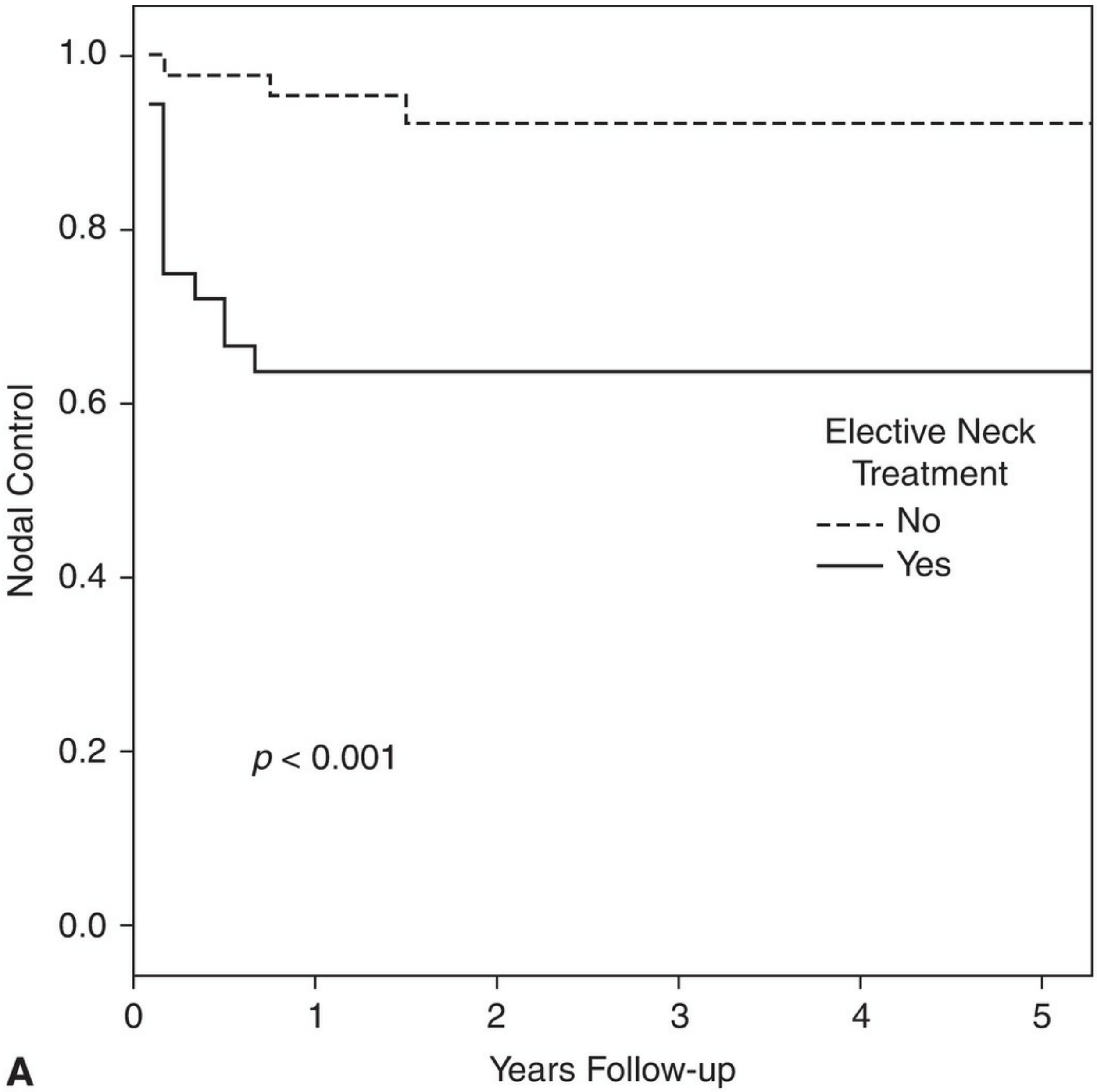


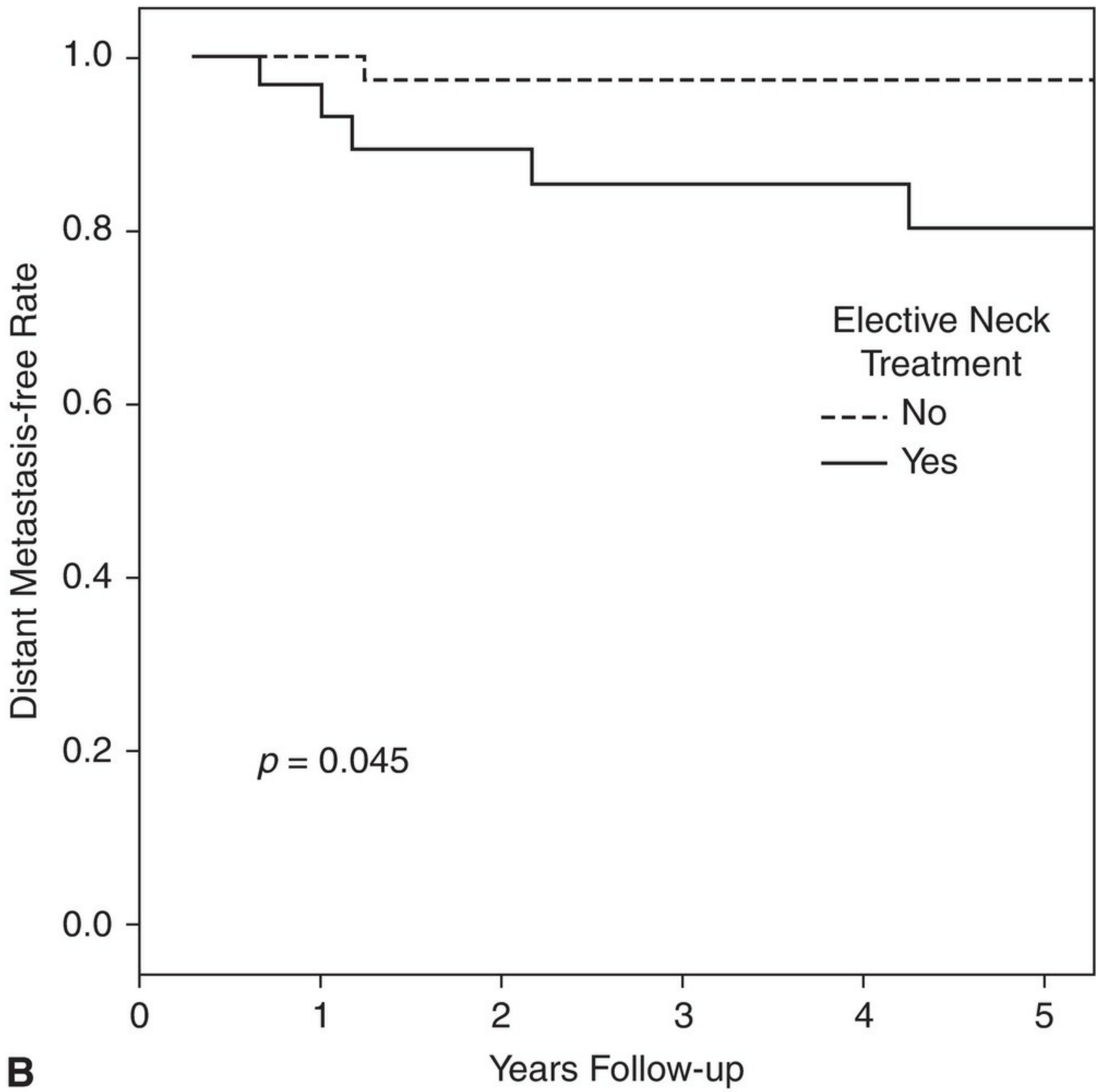
Figure 10.47. Overall survival in patients with sinonasal cancer stratified by presenting T stage and nodal status.

Obviously, patients with clinically positive lymph nodes require treatment of the neck, but prophylactic treatment of N0 patients remains controversial.[83] Because the risk of nodal metastasis is higher in patients with high-grade and advanced stage disease, it is generally recommended that the neck is electively treated in such patients. This policy of elective neck irradiation (ENI) of patients with advanced stage and high-grade tumors was adopted at MDACC in 1991.[37] **Figure 10.48A** shows the effect of elective neck RT on nodal control for node-negative (N0) patients with squamous cell or undifferentiated carcinoma. Of the 36 patients in whom the ipsilateral neck

was left untreated, 13 (36%) developed nodal recurrence versus only 3 (7%) of the 45 patients in whom ENI was administered ($p < 0.001$). The use of elective neck treatment in these patients translated into a significant reduction in distant metastases (3% in treated vs. 20% in untreated at 5 years; $p = 0.045$) and an increase in recurrence-free survival (67% in treated vs. 45% in untreated at 5 years; $p = 0.025$) (**Fig. 10.48B and C**).



A



Distant Metastasis-free Rate
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Years Follow-up
Elective Neck Treatment
No
Yes
p = 0.045

B

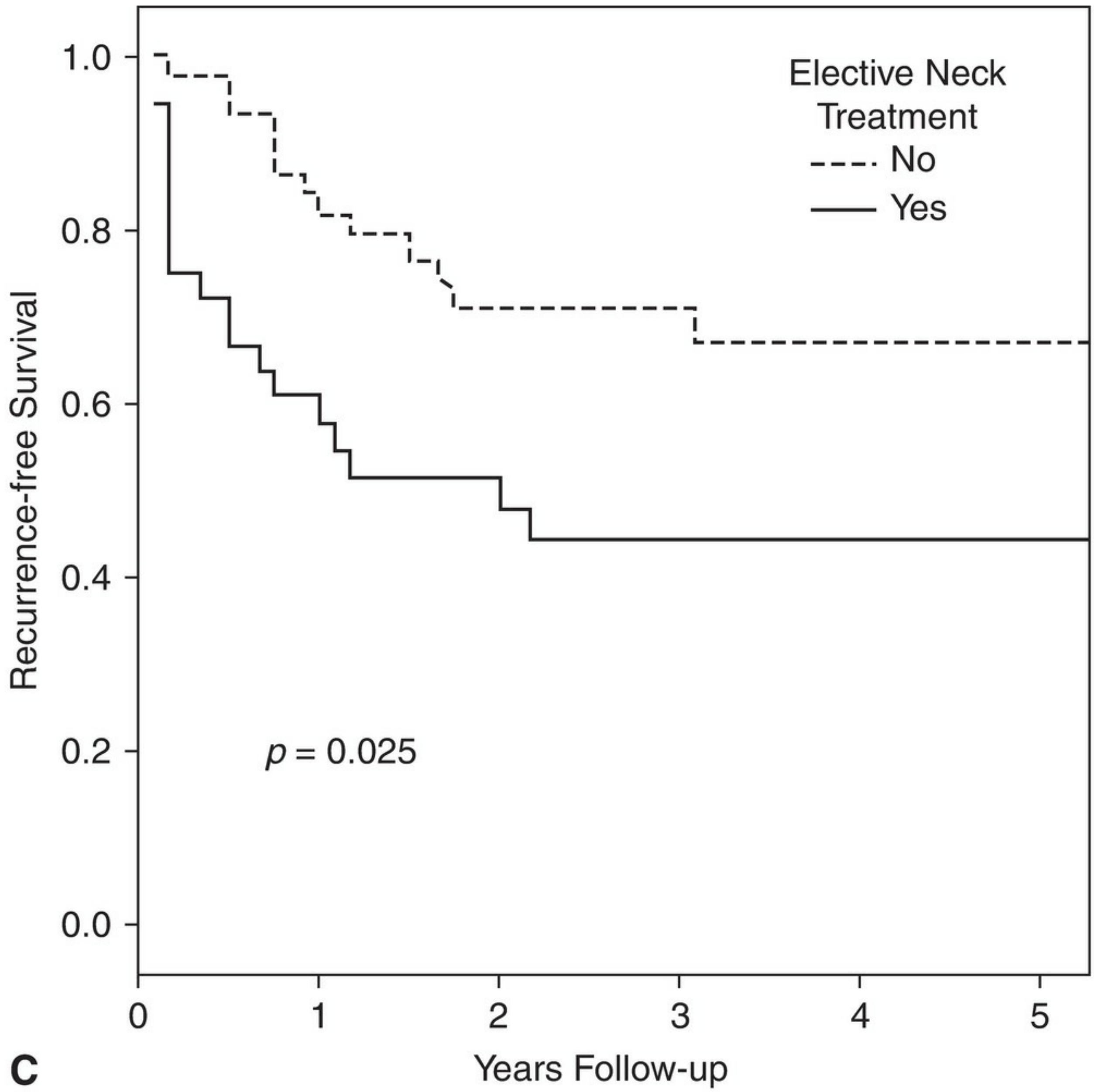


Figure 10.48. A–C: Nodal control, distant metastasis-free survival, and recurrence-free survival rates for patients with squamous cell or undifferentiated carcinoma treated with (*n* = 45) or without (*n* = 36) elective neck irradiation.

RADIATION THERAPY

Radiation therapy is frequently incorporated in the overall management of patients with cancer of the nasal cavity and paranasal sinuses. Radiation therapy may be given with curative intent, or as an adjuvant therapy before,

or after surgery. Radiation therapy may also be combined with chemotherapy either as definitive treatment or as an adjunct to planned surgical resection. Radiation therapy may also be used in the palliation of recurrent or unresectable tumors. Regardless of the treatment strategy, there is almost a universal agreement that patients with advanced stage tumors are best treated with multimodal therapy including surgery, radiation, and in some cases chemotherapy.[84,85]

Surgery followed by postoperative radiation therapy has been the accepted gold standard for most tumors of the sinonasal cavity. Hoppe et al.[86] published an 18-year experience at Memorial Sloane-Kettering Cancer Center with 85 patients treated with surgical resection and postoperative radiation for sinonasal cancers. Most patients had SCC, T4 tumors, and tumors involving the maxillary sinus. Their 5-year estimates of local progression-free, disease-free, and overall survival (OS) rates were 62%, 55%, and 67%, respectively. The authors noted that squamous cell histology and cribriform plate involvement were independent predictors for local recurrence.

There is strong evidence that the use of combined surgery and adjuvant radiation therapy results in better tumor control and survival compared to radiation alone in patients with cancer of the paranasal sinuses.[87] In 2009, Mendenhall et al.[85] reported the results of 109 patients with sinonasal cancer treated between 1964 and 2005. Within this group, 56 patients were treated with definitive radiation therapy, whereas 53 patients received surgery and postoperative radiation. Although the 5-year local control rate was 82% in patients with T1 to T3 lesions, those patients with T4 disease had a lower local control rate of 50%. Local control at 5 years was 43% after definitive radiation therapy versus 84% with primary surgery and adjuvant radiation therapy ($p < 0.0001$). Cause-specific survival rates were 81% and 54% for stages I to III and stage IV disease, respectively. This group concluded that the probability of local control and cause-specific survival is better after surgery and radiation therapy compared with definitive radiation therapy. However, selection bias may have influenced the poor results of radiation therapy given that surgery was likely performed only for patients who had resectable disease. Similarly, in 2009, Snyers et al.[88] reported a series of 168 patients treated between 1986 and 2006. In all, 130 patients were treated with curative intent by surgery followed by postoperative radiotherapy, and 38 were considered inoperable and received radiotherapy alone ($n = 21$) or

radiotherapy and chemotherapy (n = 17). For the entire population, the 5-year local control rate was 62% and regional control was 79%. Distant metastasis–free survival was 79%. Of the cases with SCC or adenocarcinoma, patients with stages I to III versus stage IV disease had a local control rate at 5 years of 79% and 54%, respectively, comparable with the series reported by Mendenhall and colleagues.[85]

External beam radiation or brachytherapy or both may be used as definitive local therapy in selected patients with early-stage cancers of the nasal cavity.[89] Primary radiation therapy however has not been a well-accepted approach for definitive treatment of more advanced sinonasal cancers. This conclusion was partly based on the poor outcomes for patients with advanced lesions and concerns that radiation therapy does not adequately treat bony invasion, which is a frequent finding in patients with sinonasal malignancies. In additions, several publications have reported increased incidence of radiation-associated optic nerve injury and osteoradionecrosis when radiation therapy is administer as primary treatment.[85,88] Although some authors propose primary concurrent chemoradiation therapy for this site,[38,90] the majority of the published data on primary radiation therapy have been for tumor deemed not surgically resectable and with a selection bias toward advanced disease.[85,88,91] In a study from Memorial Sloane-Kettering Cancer Center, the 5-year disease-free survival (DFS) and OS were 14% and 15%, respectively, for 39 patients with unresectable stage IVB paranasal sinus carcinomas treated with RT, with or without chemotherapy.[92] The majority of the recurrence (64%) was within the irradiated field. The investigators report that the only significant factor for improved local progression–free survival (LPFS) and OS was a biologically equivalent dose of radiation of >65 Gy and that treatment outcomes for patients with unresectable sinonasal malignancies remain poor.

Delivering effective doses of radiation (60 to 70 Gy) for treatment of advanced sinonasal cancer using conventional radiotherapy is associated with serious morbidity, including blindness, brain necrosis, radiation-induced endocrinopathy attributed to hypothalamic–pituitary radiation damage, and osteoradionecrosis.[85,88] The use of 3-dimensional conformal radiotherapy (3D-CRT) and IMRT increases treatment accuracy by delivering tumoricidal doses to the tumor bed while reducing radiation doses to nearby critical structures such as the optic nerves and the brain. Duprez et al.[93] examined the

ocular complications of IMRT. They reported on 130 patients treated with IMRT up to 70 Gy, of which 101 patients were in the postoperative setting. The 5-year local control and OS were 59% and 52%, respectively. There was no radiation-induced blindness in 86 patients available for the 6-month follow-up. Ten patients reported grade 3 tearing and one patient with grade 3 visual impairment from ipsilateral retinopathy and neovascular glaucoma. Brain necrosis and osteoradionecrosis occurred in six patients and one patient, respectively. Chen et al.[94] analyzed 127 patients treated between 1960 and 2005. The cohort was treated with conventional RT in 59, 3-D conformation in 45 and IMRT in 23 patients. The 5-year OS, LC, and DFS were not significantly different when analyzed by decade. However, the incidence of grade 3 to 4 toxicity was 53%, 45%, 39%, 28%, and 16% for patients treated in 60s, 70s, 80s, 90s, and 2000s. The authors conclude that improvements in therapeutic ratio were responsible for decreasing incidence of complications for patients treated throughout these decades.

More recently charged particle radiation using beams of protons, carbon ions, helium ions, or other charged particles holds promise of further enhancing high-dose delivery to tumor targets while limiting toxicity to normal tissue. The unique physical properties of charged particle therapy—with rapid fall-off of dose beyond the Bragg peak (a sharp deposition of dose at a specific depth in tissue)—and its greater relative biologic effectiveness compared with photon therapy might further augment treatment outcomes, not only by reducing the incidence and severity of complications but also by allowing an escalation in radiation dose to improve tumor control and survival, which cannot be achieved with photon therapy. A recent systematic review and meta-analysis compared the clinical outcomes of patients treated with charged particle therapy with those of individuals receiving photon therapy.[95] The study included 43 cohorts from 41 noncomparative observational studies of which 30 cohorts were treated with photon therapy (1,186 patients), whereas 13 received charged particle therapy (286 patients). Median follow-up for the charged particle therapy group was 38 months (range 5 to 73) and for the photon therapy group was 40 months (14 to 97). The pooled event rate of OS for charged particle therapy was significantly higher than that for photon therapy at the longest duration of follow-up (relative risk 1.27, 95% CI, 1.01 to 1.59; $p = 0.037$) and at 5 years (1.51, 1.14 to 1.99; $p = 0.0038$; **Table 10.5**). Locoregional control was also significantly better at the longest duration of follow-up for patients treated with charged

particle therapy than for those receiving photon therapy (1.18, 1.01 to 1.37; $p = 0.031$), but not at 5 years (1.06, 0.68 to 1.67; $p = 0.79$). The pooled 5-year DFS event rate was significantly higher for charged particle therapy than for photon therapy (1.93, 1.36 to 2.75; $p = 0.0003$) but not at longest follow-up (1.51, 1.00 to 2.30; $p = 0.052$). **Table 10.6** shows the comparison of primary outcomes for cohorts receiving proton beam therapy versus those given IMRT. DFS at 5 years and locoregional control at longest follow-up were significantly higher in the proton beam therapy group. However, no other difference was noted between proton beam therapy and IMRT.

Table 10.5 Comparison of Primary Outcomes for Charged Particle Therapy Cohorts and Photon Therapy Cohorts

	Cohorts (*n*)	Patients (*n*)	Event Rate (95% CI)	I^2	Relative Risk (95% CI)	*p*	NNT[a](S5% CI)
Overall survival[b]							
CPT	10	242	0.66 (0.56–0.79)	77.5%	1.27 (1.01–1.59)	0.037	7.09 (3.57–480.55)
Photon therapy	26	1,120	0.52 (0.46–0.60)	66.0%			
5-year overall survival							
CPT	6	146	0.72 (0.58–0.90)	80.1%	1.51 (1.14–1.99)	0.0038	4.12 (2.37–15.60)
Photon therapy	15	779	0.48 (0.40–0.57)	64.1%			
Disease-free survival[b]							
CPT	3	78	0.67 (0.48–0.95)	79.4%	1.51 (1.00–2.30)	0.052	
Photon therapy	8	411	0.44 (0.35–0.56)	76.5%			
5-year disease-free survival							
CPT	2	58	0.80 (0.67–0.95)	41.6%	1.93 (1.36–2.75)	0.0003	2.60 (1.74–5.15)
Photon therapy	6	341	0.41 (0.30–0.56)	80.9%			
Locoregional control[b]							
CPT	10	208	0.76 (0.68–0.86)	54.0%	1.18 (1.01–1.37)	0.031	8.55 (4.40–143.44)
Photon therapy	14	736	0.65 (0.59–0.71)	60.3%			
5-year locoregional control							
CPT	3	58	0.66 (0.43–1.02)	81.2%	1.06 (0.68–1.67)	0.79	
Photon therapy	8	546	0.62 (0.55–0.71)	73.0%			

From Patel SH, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lancet Oncol*. 2014;15(9):1027–1038.

I^2 ≥50% suggests high heterogeneity across studies. CPT, charged particle therapy; NNT, number needed to treat.

[a]Calculated when the difference between CPT and photon therapy was significant.

[b]At longest duration of complete follow-up.

Table 10.6 Comparison of Primary Outcomes for Proton Beam Therapy Cohorts and Intensity-Modulated Radiation Therapy Cohorts

	Cohorts (*n*)	Patients (*n*)	Event Rate (95% CI)	I^2	Relative Risk (95% CI)	*p*
Overall survival[a]						
PBT	8	191	0.63 (0.53–0.76)	59.3%	1.02 (0.77–1.35)	0.69
IMRT	8	348	0.62 (0.50–0.77)	86.9%		
5-year overall survival						
PBT	5	124	0.66 (0.52–0.85)	69.7%	1.39 (0.99–1.94)	0.057
IMRT	4	212	0.48 (0.38–0.60)	45.1%		
Disease-free survival[a]						
PBT	2	58	0.49 (0.21–1.16)	83.6%	0.98 (0.40–2.42)	0.97
IMRT	3	187	0.50 (0.38–0.67)	69.3%		
5-year disease-free survival						
PBT	1	36	0.72 (0.59–0.89)		1.44 (1.01–2.05)	0.045
IMRT	3	187	0.50 (0.38–0.67)	69.3%		
Locoregional control[a]						
PBT	7	147	0.81 (0.71–0.92)	55.2%	1.26 (1.05–1.51)	0.011
IMRT	4	258	0.64 (0.57–0.72)	33.7%		
5-year locoregional control						
PBT	2	36	0.43 (0.09–2.10)	89.5%	0.73 (0.15–3.58)	0.70
IMRT	2	166	0.59 (0.52–0.67)	0.0%		

I^2 ≥50% suggests high heterogeneity across studies. IMRT, intensity-modulated radiation therapy; PBT, photon beam therapy.

[a]At longest duration of complete follow-up.

CHEMOTHERAPY

In an effort to improve local control and survival rates, chemotherapy is being increasingly incorporated in the management of patients with cancer of the SNT and cranial base. Chemotherapy has been included in the treatment of SCC, SNUC, NEC, ENB, and SG carcinoma of the paranasal sinuses. Chemotherapy may be given as induction (neoadjuvant), adjuvant, maintenance, or palliative treatment. It may be combined with radiation in a sequential or concurrent fashion. Routes of administration include systemic (intravenous or oral), regional (intra-arterial), and local (topical).

The incorporation of chemotherapy with radiation in a multimodality treatment approach seems to further enhance local control and perhaps DSS in patients with advanced- or high-grade cancer of the SNT. In the neoadjuvant setting, the most frequently used agents are cisplatin based, as a

single agent or in combination with one of the following agents: docetaxel, etoposide, ifosfamide, 5-fluorouracil, and cetuximab. (For pathology-specific regimens, please refer to next section in this chapter.) Potential benefits of induction chemotherapy are that it improves distant control, provide prognostic information, can cytoreduce tumors, and improve radiotherapy and surgical feasibility and tolerability.[78,96,97] Excellent long-term local control, OS, and DFS were achieved in locoregionally advanced paranasal sinus cancer treated with induction chemotherapy, followed by surgery and postoperative concomitant chemoradiotherapy.[96] Induction chemotherapy achieved a clinical response in 87% of patients, and a complete histologic response was documented at the time of surgery in half of these patients. The 10-year OS, DFS, and local control rates were 56%, 73%, and 79%, respectively. These results are encouraging and may be superior to those achieved with surgery and radiation therapy. Further investigation of incorporating chemotherapy with radiation and surgery in a multimodal approach is warranted.[96] More recently, Hanna et al.[78] reviewed the oncologic outcomes of patients with advanced SCC of the paranasal sinuses treated with induction chemotherapy prior to definitive local therapy at MDACC. All patients had T3 or T4 tumors, and 12 (26%) patients had clinical evidence of nodal metastasis, with an overall stage of III (20%) or IV (80%). More than two-thirds (67%) of the patients achieved at least a partial response to induction chemotherapy, 24% had progressive disease, and 9% had stable disease. Subsequent treatment after induction chemotherapy consisted of surgery usually followed by radiation or chemoradiation or by definitive radiation or chemoradiation with surgical salvage of any residual disease. Overall, surgical resection was performed in only 24 of 46 patients (52%) treated with induction chemotherapy. The 2-year survival for patients with at least a partial response or stable disease after induction chemotherapy was 77% in contrast to only 36% for patients with progressive disease (**Fig. 10.49**). The authors concluded that tumor response to induction chemotherapy in patients with advanced SCC of the paranasal sinuses may be predictive of treatment outcome and prognosis. Favorable response to induction chemotherapy is associated with better survival and a reasonable chance of organ preservation.[78]

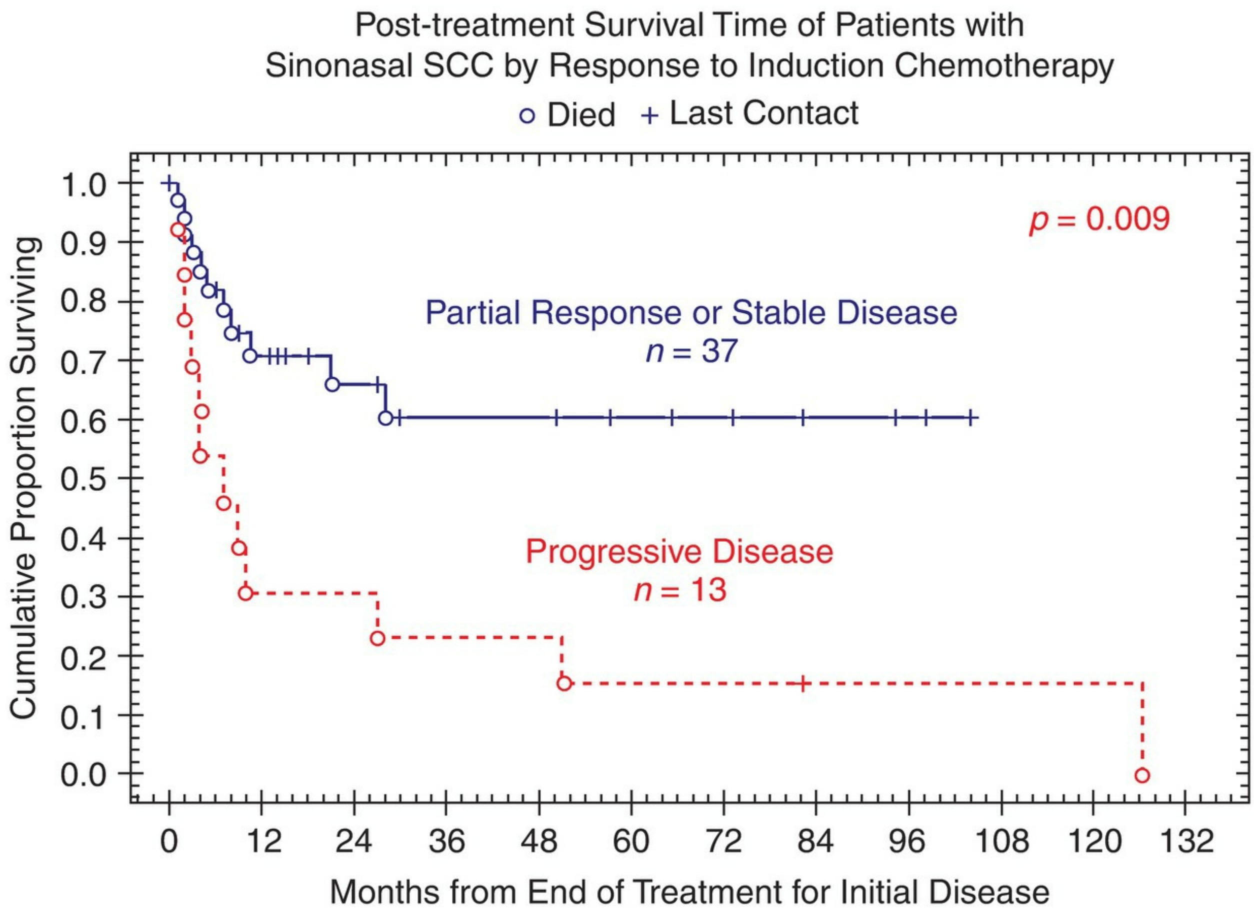


Figure 10.49. Survival in patients with sinonasal SCC by response to induction chemotherapy. (Hanna EY, et al. Induction chemotherapy for advanced squamous cell carcinoma of the paranasal sinuses. Arch Otolaryngol Head Neck Surg. 2011;137(1):78–81, Ref. 78.)

Intra-arterial chemotherapy has been proposed with the intention of limiting radiation doses to critical structures and organ preservation. The University of Tennessee reported on 19 patients with advanced stage tumors (84% with T4 disease) treated by intra-arterial high-dose cisplatin with concurrent radiation therapy followed by organ-sparing surgery.[90] The OS at 2 and 5 years was 68% and 53%, respectively. Ten patients developed grade 3 mucosal toxic effect, three patients with hematologic toxic effect, and one patient developed confusion. One patient developed a treatment-limiting toxic effect (died of myocardial infarction). Homma et al.[98] reported similar favorable oncologic results in 47 patients treated with intra-arterial cisplatin and conventional external-beam radiotherapy (65 to 70 Gy). The 5-year OS rate was 69.3% for the cohort. 74.5% experienced grade 3 to 4 toxicity. There

were 25 late adverse reactions: osteonecrosis (*n* = 7), brain necrosis (*n* = 2), and ocular/visual problems (*n* = 16). The authors concluded that this regimen can cure the majority of patients with advanced tumors and facilitate organ preservation, but late adverse reactions need to be monitored in future studies.

Topical chemotherapy has been reported to have favorable results in the treatment of adenocarcinomas of the ethmoid sinuses. The regimen usually involves surgical debulking followed by a combination of repeated topical chemotherapy (5-fluorouracil) and necrotomy. The 5-year DFS has been reported in the range of 85%, comparable to surgery with postoperative radiation therapy.[99,100] Several reports from Japan described the use of regional or local chemotherapy in addition to radiation to reduce the extent of surgical resection of maxillary sinus cancer and demonstrated equal (and sometimes better) cure rates compared to conventional treatment consisting of radical surgery followed by radiation therapy. For example, a report described the outcome of 75 patients with cancer of the maxillary sinus treated with surgery through a sublabial incision and tumor debridement, radiotherapy, and regional chemotherapy.[101] All 23 patients with orbital involvement retained the orbital contents, and the majority demonstrated adequate ocular function. The authors concluded that combined therapy with conservative surgery, radiotherapy, and regional chemotherapy appears to be an effective method for local control and the preservation of ocular function.[101]

Tumor-Specific Considerations

Squamous Cell Carcinoma.

SNSCC is the most common histologic subtype and accounts for almost half of all cancer in the sinonasal region. Of the 2,698 patients with sinonasal cancers treated at MDACC, 45% had SNCC (Fig. 10.12D). A recent comprehensive analysis using the United States National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database registry reported the trends in the epidemiology of SNSCC.[102] A total of 4,994 cases of SNSCC were identified, composed of 65% males and 35% females amounting to a 1.81:1 male-to-female prevalence ratio. The majority of SNSCC tends to occur in people 55 years and older, with 3,954 (79%) cases

reported in patients older than 55. Dividing the data by race showed that 4,120 (82.50%) patients were white, 436 (8.73%) were “others,” and 438 (8.77%) were black. The majority of cases reported the paranasal sinuses (2,693 cases, 53.92%) as the primary sites with the remainder of cases being in the nasal cavity (2,301 cases, 46.08%). Incidence trend analysis revealed a significant decrease in yearly rates from 1973 to 2009 for the overall population, females, whites, blacks, and “others” ($p < 0.05$). This decrease may be partially attributable to decreased exposure to textile dust and heightened awareness and better regulation of the exposure to the carcinogenic effect of industrial substances. Another variable that may have contributed to the decrease in overall incidence of SNSCC is the decline in tobacco smoking.[102]

The majority of SCC of the paranasal sinuses is keratinizing, but tends to be only moderately differentiated. Nonkeratinizing and poorly differentiated carcinomas are less common, and the latter show a more rapid course of growth. Variants of SCC make up 15% of all cases of SCC of the upper aerodigestive tract. There are five main histologic variants of SCC in the head and neck region: verrucous (VSCC), papillary (PSCC), spindle cell (sarcomatoid) (SCSC), basaloid (BSCC), and adenosquamous (ASC). Conventional sinonasal SCC has been studied extensively, but far less is known about its major variants. In a recent SEER database analysis, a total of 4,382 cases of conventional sinonasal SCC and 328 cases of its major variants were found.[103] Sinonasal BSCC was diagnosed at a significantly lower mean age than sinonasal SCC. Sinonasal SCSC significantly affected the maxillary sinus more commonly than SCC. In the setting of advanced stage disease, sinonasal VSCC, PSCC, and BSCC appear to be associated with a better prognosis than conventional sinonasal SCC, whereas the impact of histologic subtype on prognosis in early-stage disease appears to be more limited. Survival for SCSC and ASC, both regarded as more lethal variants, was statistically similar to conventional SCC. This study highlights the importance of distinguishing between conventional sinonasal SCC and its major histologic variants, because histologic subtype appears to carry important prognostic implications.[103]

Another distinct entity is schneiderian carcinoma, which commonly represents malignant transformation in a preexisting schneiderian papilloma (SP). Carcinomas arising from SP are rare, with more carcinomas identified

in the inverted type and oncocytic types, with only isolated reports describing carcinomas arising from the exophytic type. Carcinoma ex-SP ranges from 2% to 27% in the literature, but in a recent systematic review, without referral or academic institution bias, the 1.9% rate may be a more accurate rate.[104] In general, the male to female ratio of patients with schneiderian carcinoma ranges from 1.2 up to 6.7, with an overall average of about 3.4:1. Patients range in age from 32 to 86 years, with an overall mean around 61 years. Most patients experienced a mixed anatomic site presentation: nasal cavity combined with maxillary, ethmoid, sphenoid, and/or frontal sinus, with possible involvement of the nasopharynx and ear. SCC is the most common carcinoma type (85%), with other carcinoma types (mucoepidermoid, SNUC, and carcinoma, not otherwise specified [NOS]) less frequent. The role of human papilloma virus (HPV) in the oncogenesis of SP and malignant transformation remains to be defined, but some studies have demonstrated that high-risk HPV is more prevalent in dysplastic SP and in those with malignant transformation.[105,106] The majority of schneiderian carcinomas are synchronous (carcinoma present at primary presentation of SP) with 36% metachronous (carcinoma developing after initial treatment of SP). This highlights the importance of complete excision and careful histopathologic assessment of all SP, which minimizes the risk of recurrence and allows comprehensive evaluation of the specimen for the presence of any coexisting malignancy.[107] The recurrence rates of SP quoted in the literature vary from <5% to as high as 75% and may depend on the surgical approach and the completeness of the surgical excision. Although multicentricity of the tumor has been suggested to be responsible for the high rate of recurrence, inadequate removal of the tumor during the initial resection seems to be the most important predictive factor of local recurrence. This was well demonstrated by Myers et al.[108] who reported <5% recurrence rate of adequately resected SP.

The majority of patients with SNSCC (85%) present with advanced stage (T3 to T4) cancer. Although the reported incidence of clinically evident lymph node metastasis presentation is around 10% to 15%, the overall risk of nodal involvement from SCC of the paranasal sinuses is closer to 30%.[37,109] Regional spread to the lymph nodes is uncommon in cancer confined within the sinus walls. Once invasion into the overlying soft tissue and adjacent structures occurs (e.g., the oral cavity), nodal involvement and even

dissemination to distant sites are noted more frequently. Distant metastasis can be present in up to 10% of patients on initial diagnosis.[110]

Treatment of SNSCC depends on the stage and extent of disease. Early-stage (T1 to T2) tumors can be treated by single modality therapy more commonly surgery or in some selected cases radiation therapy. Patients with localized disease showed 5-year survival rates of 86%, 80%, and 78% when receiving surgery, radiation and surgery, and radiation alone, respectively.[102] Endoscopic sinus surgery may be applied in selected cases as discussed earlier with relatively good outcomes that are comparable to open surgery[54,69,111] (Fig. 10.24). The majority of patients with more advanced and resectable disease are treated with surgery and postoperative radiation. Extension to the skull base is common, and craniofacial resection has enhanced our ability to resect locally advanced tumors successfully.[45,46,112]

Lymph node metastases signify more advanced disease and carry worse prognosis. The reported incidence of lymph node metastasis at presentation varies from 10% to 15%, and nodal recurrence may occur in as much as 30% of patients.[83] The most common sites of involvement are the retropharyngeal and level II nodes. In cases where the primary disease can be addressed surgically and there is clinical evidence of nodal metastasis, a therapeutic nodal dissection should be performed. Management of the clinically N0 neck remains controversial, but elective nodal irradiation may be warranted in patients with locally advanced disease.[36,37,82,109]

Locally advanced disease that is not surgically resectable can be managed with radiation or chemoradiation therapy. Radiation therapy alone in this setting yielded poor results, and more promising outcomes have been reported by the use of intensive regimens of chemotherapy followed by concurrent chemoradiation.[96] In a review of 46 patients with locally advanced SNSCC treated with neoadjuvant chemotherapy at MDACC, more than two-thirds (67%) of the patients achieved at least a partial response to induction chemotherapy, and an additional 9% had stable disease.[78] The 2-year survival for patients with at least a partial response or stable disease after induction chemotherapy was 77% in contrast to only 36% for patients with progressive disease (Fig. 10.49).

Several recent reviews report an improvement in 5-year OS between 30% and 60%.[102,110,111] The most significant predictor of survival remains disease

stage with 5-year OS for localized, regional, and distant disease being 83%, 41%, and 29%, respectively.[102] Recurrence after treatment occurs most frequently locally (36% to 69%), followed by regional (27% to 33%) and distant (15% to 35%).

To improve our understanding of the biologic features of SNSCC and to promote development of novel therapeutic strategies for this disease, identification of new molecular markers is essential. Because of the rarity of this tumor, however, few molecular studies have been done.[35] We recently reported a comprehensive study of molecular markers in tumor specimens from 70 patients treated at MDACC for SNSCC, by using tissue microarrays to explore new useful prognostic markers or novel therapeutic targets.[20] The markers we evaluated included HR-HPV and its surrogate marker p16, the well-known cyclin-dependent kinase inhibitor p16Ink4A; cyclin D1, a key factor for cell cycle G1/S transition; 3 receptor tyrosine kinases, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and c-Kit; tumor suppressor p53 and its downstream proapoptotic protein Bax; matrix metalloproteinases (MMP)-2 and MMP-9, which are known to be associated with tumor invasion and metastasis; vascular endothelial growth factor (VEGF), which stimulates vasculogenesis and angiogenesis; and DNA repair proteins Ku70 and excision repair cross-complementing 1 (ERCC1). EGFR, cyclin D1, MMP-2, MMP-9, Ku70, and ERCC1 were positive in more than half of the specimens. p16 Ink4A, VEGF, p53, and Bax were expressed in 10% to 40% of cases. For all of the markers except HR-HPV, HER2, and c-kit, differences in expression between normal and tumor tissues were significant by two-tailed Fisher exact test. The most significant finding in this study was that patients with EGFR-positive SNSCC had a significantly poorer rate of DFS than patients with EGFR-negative disease (p = 0.01307) (**Fig. 10.50A**). Their OS rate was worse as well, but the difference was not statistically significant (p = 0.06398) (**Fig. 10.50B**). The rate of local recurrence was significantly worse for patients with EGFR-positive disease (p = 0.0144). In summary, this study showed that EGFR protein expression may be a prognostic indicator for SNSCC. If this finding is confirmed by further studies, targeted inhibition of EGFR may be a new approach to treating patients with SNSCC.[20]

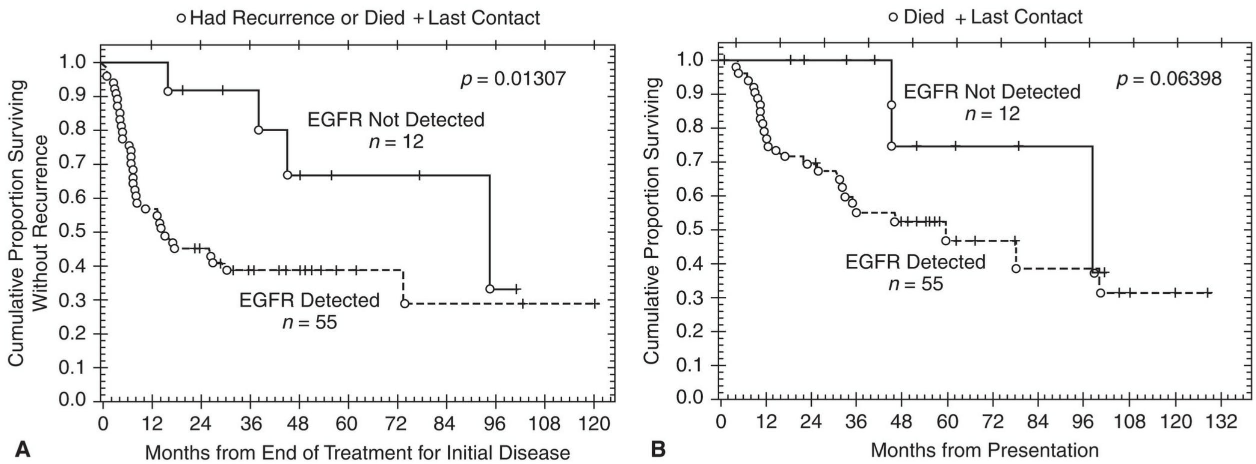


Figure 10.50. Kaplan-Meier analyses of survival of patients with sinonasal SCC according to EGFR expression. **A:** Patients with an EGFR-positive tumor had significantly shorter DFS than patients whose tumor did not express EGFR ($p = 0.01307$). **B:** Patients with an EGFR-positive tumor had a poorer OS rate than patient whose tumor did not express EGFR, but the difference was not statistically significant ($p = 0.06398$). (Takahashi Y, et al. Comprehensive assessment of prognostic markers for sinonasal squamous cell carcinoma. Head Neck. 2014;36(8):1094–1102, Ref. 20.)

Adenocarcinoma.

The World Health Organization classifies primary SNACs into salivary and nonsalivary types. Salivary types are usually well-defined myoepithelial neoplasms, which closely resemble their salivary counterparts. The most common type is ACC, and other types of salivary adenocarcinomas are rare in the SNT, but cases of acinic cell carcinoma, MEC, epithelial–myoepithelial carcinoma, basal cell adenocarcinoma, salivary duct carcinoma, polymorphous low-grade adenocarcinoma (terminal tubulus adenocarcinoma), and carcinoma-ex-pleomorphic adenoma have been reported.[114] Nonsalivary types are separated into intestinal-type SNAC (ITAC) and non-ITAC, and both have low- and high-grade categories.[115] ITACs are aggressive tumors and often arise in the ethmoid sinus. The lesions closely resemble adenocarcinomas of the large intestine with papillae and infiltrating glands lined by tall, columnar epithelial cells with hyperchromatic elongated nuclei. Goblet cells, Paneth cells, and endocrine cells are sometimes present, and a variable amount of extracellular mucus is seen. They are divided into well differentiated (papillary, tubular, and

papillary–tubular type), moderately differentiated (papillary–mucinous and papillary–tubular–mucinous type), and poorly differentiated (mucinous, alveolar goblet cell, signet-ring type).[9] Non-ITACs are somewhat poorly characterized and have been less reported.[116] They are of presumed seromucous gland origin, have marked morphologic heterogeneity, and can arise anywhere in the SNT. Moreover, ITACs typically demonstrate an intestinal-type immunohistochemical profile (CK20+, CK7−, CDX2+, and villin+), whereas non-ITACs reveal a respiratory-type profile (CK20−, CK7+, CDX2−, and villin−).[115]

SNAC is the second most common malignant tumor of the SNT after SCC. It accounts for ~10% to 20% of all sinonasal cancers.[117] However, SNACs have been reported to be the most common pathology in European series. The reason for this is unclear but may be related to increased occupational exposure particularly in the wood industry.[6,8] There is a strong association with wood dust exposure and leather tanning; between 45% and 90% of cases demonstrate prolonged exposure with a mean duration of ~22 to 32 years.[99,113,118–120] Recent studies suggest that this increased risk is specifically linked to the development of ITACs of the ethmoid sinuses rather than other types of SNACs.[9–11] One of the largest series from Italy involved 646 consecutive patients with malignant tumors of the paranasal sinuses that were surgically treated at the Fondazione I.R.C.C.S. Istituto Nazionale dei Tumori of Milan, between January 1987 and November 2007.[9] Among the 345 patients with ethmoid cancer, exposure to organic dusts was found in 148 of 153 patients with ITAC, in 3 of 16 patients with non-ITAC adenocarcinoma, and in 10 of 176 patients with other tumors. The authors concluded that only ethmoid ITACs have an indisputable relationship with the exposure to organic dusts.[9]

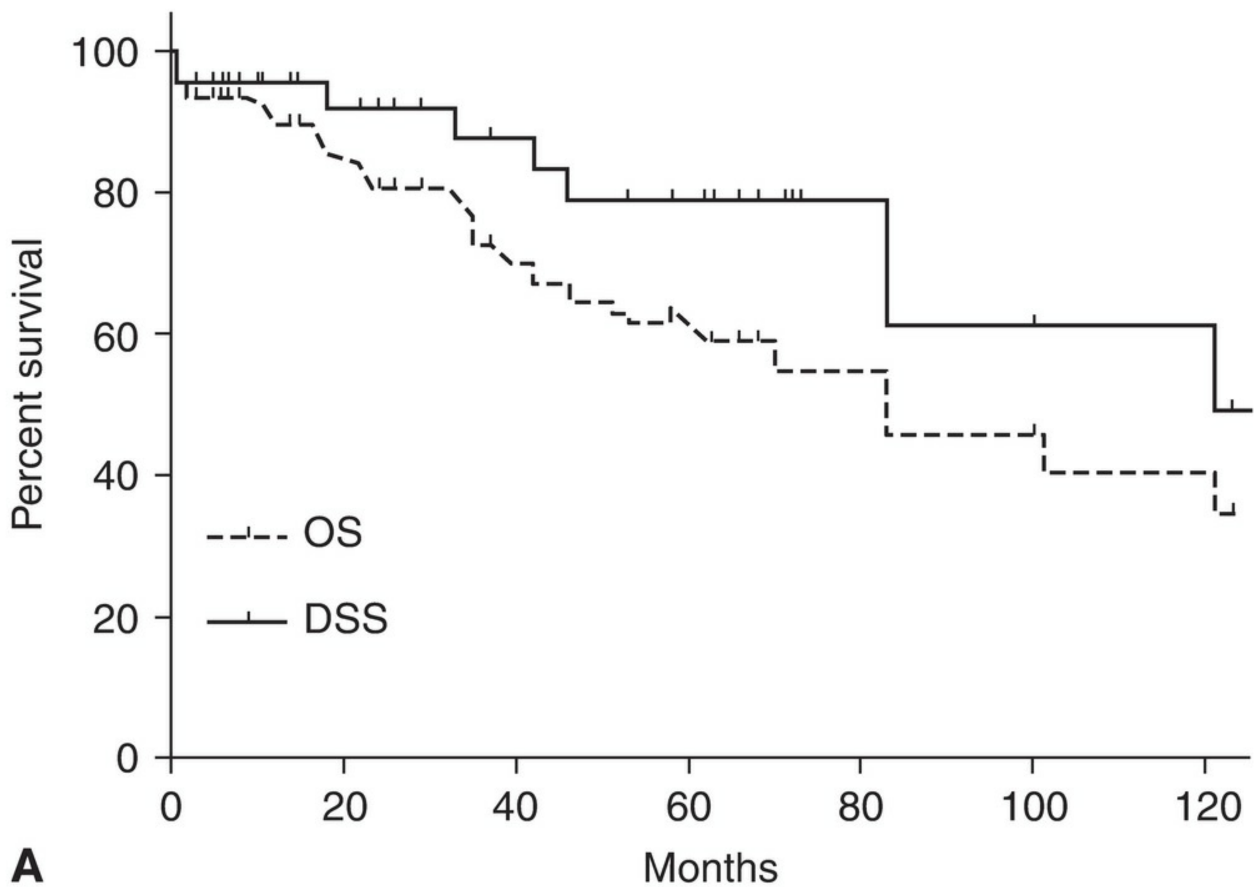
The first dedicated large-scale, retrospective analysis of a North American SNAC population reported in 2014 the demographics and survival of patients diagnosed within the time period of 1973 to 2009 using the SEER database.[121] Of the total 1,270 cases of SNAC analyzed, males accounted for 52% of cases, whereas females accounted for 48% of cases, amounting to a male-to-female ratio of 1.06:1.00. This is in great contrast to the striking male-to-female ratio of 21:1 for patients with ITACs reported from Italy by Cantu et al.[9] Age ranges from 9 to 90 years, although the average age of

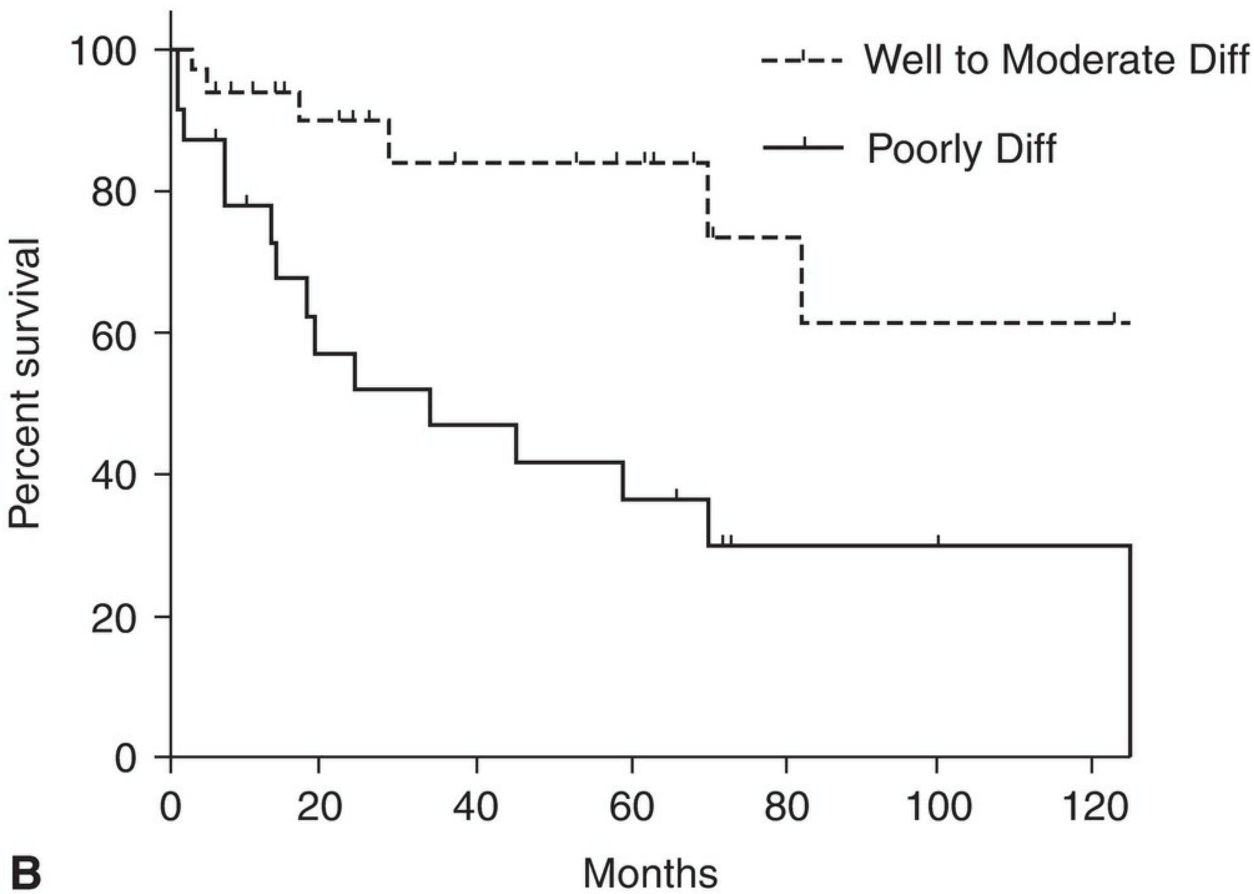
presentation is between 50 and 60 years. The most common site for nonsalivary SNACs is the ethmoid sinuses (40%), followed by nasal cavity (27%) and maxillary sinus (20%).[114] Patients tend to present with nonspecific symptoms, with nasal obstruction, epistaxis, and headache being the most common complaints.[99,113,120] Presentation is usually similar to that of inflammatory sinonasal pathology, so diagnosis may be delayed.[117] The majority of patients present with advanced disease (T3 or greater).[113]

The mainstay of treatment of SNAC is surgical resection, which can be performed through an endoscopic or open approach such as lateral rhinotomy, midfacial degloving, Caldwell-Luc, or, if the there is skull base invasion, craniofacial resection.[117] Whatever approach is used, the goal of surgery should be complete removal of the tumor with negative margins to maximize local disease control. Postoperative radiation therapy is usually used in most patients with advanced disease (T3 and T4) and can probably be avoided in smaller lesions (T1 to T2) when resection margins are wide, although the exact indications for adding radiation are not well defined and have not been studied in randomized trials. In one of the largest studies reported by the French GETTEC (Groupe d'Etude des Tumeurs de la Tête et du Cou) group, 418 patients who had presented with ethmoid adenocarcinoma at 11 French hospitals from 1976 to 2001 were analyzed to determine the clinical characteristics and treatment of the disease.[119] Treatment consisted of surgery alone in 55 cases (13.2%), radiotherapy alone in 33 cases (7.9%), and combined treatment (surgery and radiotherapy) in 324 cases (77.7%). Five (1.2%) patients received no treatment due to their poor medical status. The survival of these four groups of patients showed a higher rate of survival in groups who had been treated with surgery ($p < 0.0001$). The surgical approach was transfacial in 274 cases (72.5%), combined in 77 (20%), neurosurgical in 22 (6%), and endoscopic in 6 (1.5%). The OS rates of the population for 1, 3, 5, and 10 years were 88%, 72%, 64%, and 49%, respectively. The median survival was 120 months. A Kaplan Meier analysis showed factors that significantly negatively influenced the survival rate of this population were the size of the lesion (T4), lymph node involvement (N+), and invasion of the brain or dura, sphenoid, or orbit.

These findings were similar to studies from North America, where the distribution of non-ITACs is significantly higher than in Europe where ITACs are the predominant type. The recently published MDACC experience

with SNAC demonstrated 5-year OS of 66%, with a median survival of 83 months.[113] The 5-year DSS was 79% with median survival of 121 months (**Fig.** 10.51**A**). Histologic subtypes (ITAC 53% vs. non-ITAC 47%) did not show significant correlation with survival; however, poorly differentiated carcinomas had significantly worse survival compared with well- or moderately differentiated tumors (**Fig. 10.51B**). Similar to the GETTEC series, 5-year survival was found to be significantly worse in patients with T4 disease compared to lower T classifications (p < 0.05; **Fig. 10.51C**). Sphenoid sinus invasion also significantly correlated with worse prognosis (p = 0.013, **Fig. 10.51D**), but unlike the GETTEC series, in the MDACC study prognosis was not affected by patients who presented with skull base invasion or dural invasion (p = 0.162). Multimodality treatment regimens showed significant association with improved survival versus unimodality therapy.





Well to Moderate Diff
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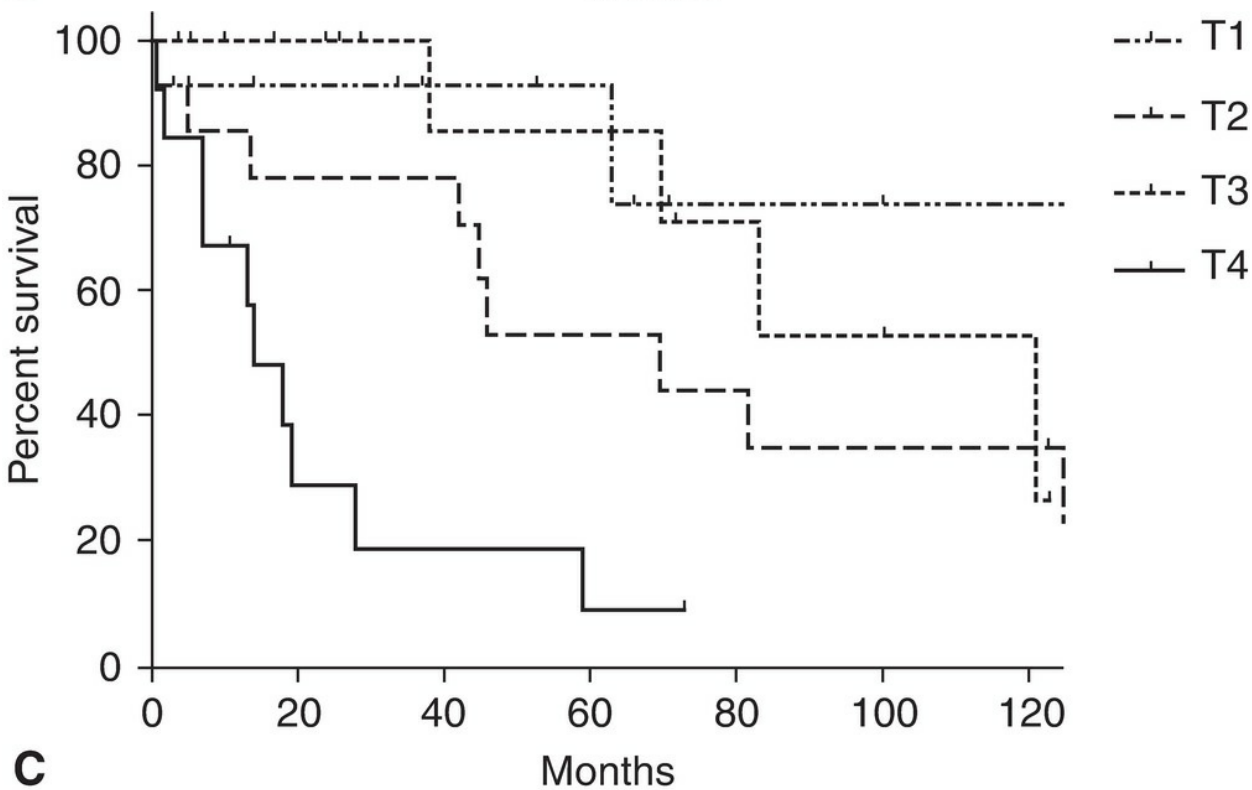

T1
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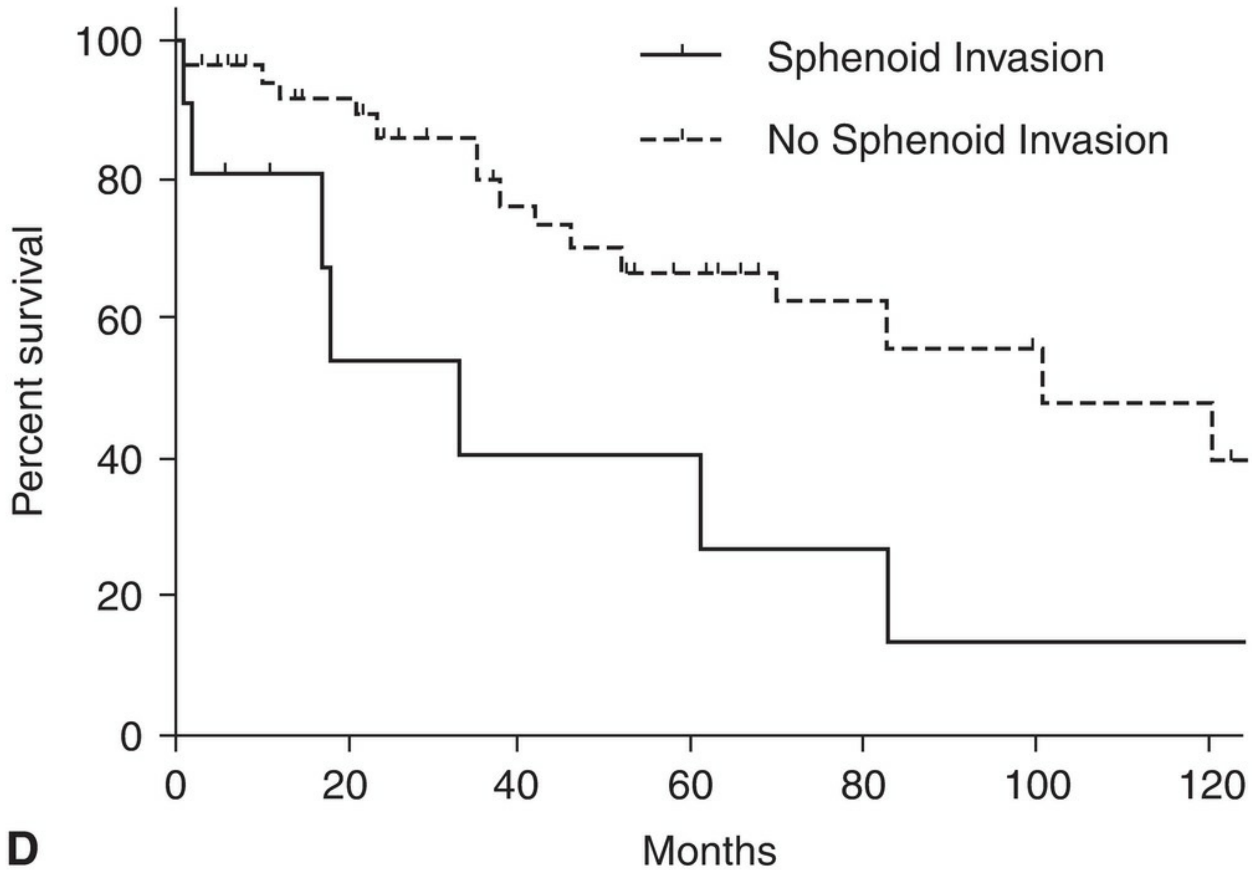


D

Figure 10.51. Outcomes of patients with SNAC. **A:** OS and DSS of patients with SNAC. **B:** Survival is significantly reduced in patients who have poorly differentiated pathology ($p = 0.002$). **C:** Survival distribution by T classification reveals T4 disease to have significantly lower survival ($p < 0.001$). **D:** Survival is significantly reduced in patients who have sphenoid sinus invasion ($p = 0.013$). (Bhayani MK, et al. Sinonasal adenocarcinoma: a 16-year experience at a single institution. Head Neck. 2014;36(10):1490–1496, Ref. 113.)

More recently, as with other types of sinonasal tumors, endoscopic resection has gained increasing popularity, and several series have reported comparable outcomes to those obtained by open approaches in well-selected patients and with appropriate use of adjuvant therapy.[54,67–69,120,122–125] In 2014, Vergez et al.[120] published a retrospective, multicenter study of nine French tertiary referral centers, of 159 patients with SNAC treated by an endoscopic approach. Histologic margins were positive in 17%. In total, 130 patients received adjuvant radiotherapy on the primary tumor site (58 Gy), 24 cases were not irradiated, and 5 refused treatment. The mean follow-up was

32.5 ± 24 months. The recurrence rate was 17.6% (28 cases) within 23 ± 21 months. Eleven patients underwent a second surgical procedure. Nine patients died of their disease (3T2, 2T3, 4T4b). The overall and disease-specific rate at 3 years was 74% and 84%, respectively. In the MDACC study of patients surgically treated for SNAC, open surgical resections did not offer a greater survival benefit compared with endoscopic procedures across all T classifications.[113] Moreover, open procedures did not significantly improve survival compared with endoscopic surgical resections when outcomes were matched for T1 to T2 (p = 0.52) and T3 to T4 (p = 0.82).

For patients with unresectable SNAC, radiation therapy alone has been used, but to date, the effectiveness of radiotherapy alone for SNAC has not been extensively studied.[126] Generally, radiotherapy as a single-modality treatment has less efficacy than that of surgery or combined therapy; however, it should be noted that patients treated with radiotherapy alone are more likely to have locally advanced incompletely resectable tumors and are not comparable to those treated with surgery. This selection bias is inherent in the literature concerning the efficacy of radiation alone as definitive treatment of patients with SNAC.[117] Promising results are evolving though from newer radiation therapy techniques. For example, a recent study by Koto et al.[126] evaluated the safety and efficacy of carbon ion radiotherapy (CIRT) for patients with locally advanced SNAC. Of the 22 patients with SNAC who were treated with CIRT, 16 patients had CIRT as primary treatment. The majority had T4 disease (5 patients had T4a and 14 patients had T4b). The median follow-up period was 43 months for all patients. The 3-year local control and locoregional control rates for all patients were 77% [95% CI, 56.7% to 97.1%] and 61% (95% CI, 38.5% to 84.1%), respectively. The 3-year OS and DSS rates were 59% (95% CI, 38.6% to 79.6%) and 66% (95% CI, 44.9% to 86.3%), respectively. The authors concluded that CIRT is effective and safe for patients with inoperable SNAC, but further studies on larger numbers of patients and long-term follow-up are needed to define the usefulness of CIRT for locally advanced SNAC.

Another approach that has been less reported for inoperable disease is surgical debulking and the use of adjuvant topical chemotherapy. Although not widely popular, there are two reports of this technique, but results are encouraging.[99,100] Knegt et al.[99] reported their strategy of surgical debulking of SNAC followed by application of topical fluorouracil (5-FU). The 5-FU

application was repeated 8 times with debridement of necrotic tissue at that time. They reported a 79% overall 5-year survival and 87% 5-year DSS. More recently, Almeyda and Capper[100] reported the outcome of 25 consecutive patients with locoregionally advanced SNAC of whom 14 patients were treated with primary radiotherapy and 11 with surgery and topical 5FU. Five-year DFS improved was 50% with primary radiotherapy and 86% with debulking surgery and topical 5FU ($p = 0.03$).

Systemic chemotherapy has also been in used in the management of advanced or metastatic SNAC. There are several reports of metastatic SNAC responding to docetaxel, cisplatin, and 5-FU.[127] Brasnu et al.[128] reported an overall response rate to neoadjuvant cisplatin and 5-FU of 36% ($n = 8$), 23% showed a complete clinical response, and 13% showed complete histologic response. In the series reported by Roux et al.[129] of 54 patients with ethmoid SNACs given neoadjuvant cisplatin and 5-FU, 8 showed complete response (15%), 12 had a >50% reduction in tumor volume (22%), and 34 had no response (63%) or <50% reduction in tumor volume. Patients who did respond fared better with 100% 10-year survival if a complete response was achieved with chemotherapy.

Adenoid Cystic Carcinoma.

ACC accounts for ~10% of all nonsquamous carcinomas in the head and neck and 15% of all tumors of the SGs. It is the second most common cancer of SGs, after MEC. ACC arises more commonly in the minor SGs than in all the major glands combined. It accounts for over 35% of all tumors involving the minor SGs. The oral cavity, including the palate, and the SNT are the most common sites representing 50% and 18% of all ACC in the minor SGs, respectively. ACC represents 3% to 15% of malignant tumors arising in the paranasal sinuses (Fig. 10.12D). It is slightly more common in females, and ~90% of patients are between 30 and 70 years of age, with a peak incidence in the fifth and sixth decades of life.[130–135]

Lupinetti et al.[25] reported a study of 105 patients with sinonasal ACC seen at MDACC from 1990 to 2004. The mean patient age at presentation was 50.8 years (range, 18 to 81 years). Most patients were Caucasians (72.4%), nonsmokers (48.4), and nondrinkers (74.4%). Common presenting symptoms included nasal obstruction, facial pain, epistaxis, nasal drainage, and facial numbness in the distribution of the second division of the

trigeminal nerve. Forty-eight percent of patients presented to MDACC after initial diagnosis of their disease, whereas 19% presented with residual disease after prior treatment, and 33% presented with recurrent disease. The site of origin of the tumor was the maxillary sinus in 46.7% of patients, the nasal cavity in 29.5%, the ethmoid sinus in 11.4%, and the sphenoid sinus in 4.8%. ACC has a propensity for perineural spread and bony invasion and at the time of initial diagnosis, 27.6% of tumors extended to the skull base, and 23.8% invaded the skull base. The majority of patients presented with T3/T4 (76.7%), N0 (98%), and M0 (97%) disease.

ACC exhibits three histologic subtypes based on tumor architecture: cribriform, tubular, and solid. The *cribriform* pattern, which is the most common subtype, has the classic “Swiss cheese appearance” in which the cells are arranged in nests separated by round or oval spaces. The *tubular* (or trabecular) pattern has a more glandular architecture, whereas the *solid* (or basaloid) pattern shows sheets of cells with little or no luminal spaces. The tubular variety has the best prognosis, the solid variety has the worst prognosis, and the cribriform pattern has an intermediate prognosis.[25] Most ACCs usually exhibit a mixed architecture of more than one pattern, and their classification in such cases depends on the predominant histologic subtype.[136]

ACC exhibits a slow growing, locally aggressive, relentless progression of disease. Patients may have symptoms from 10 weeks to 15 years prior to diagnosis, with an average of 5 years. Recurrence can occur 10 to 20 years after the initial treatment, and 5-year “survival” rates may give an erroneous indication of absolute survival. Perineural spread—the hallmark of ACC—is usually evident and provides avenues of spread to the cranial base and the central nervous system.[34] In a recent international collaborative study of 495 patients with ACC of the head and neck, of 239 patients (48%) who had nerve invasion, 174 (73%) had PNI, 65 (27%) had intraneural invasion, and 37 had (15%) perineural inflammation.[137] The maxillary, mandibular, and vidian nerves are the most frequently involved and allow perineural spread of sinonasal ACC through the foramina rotundum and ovale and the vidian canal (Fig. 10.17). Retrograde spread intracranially, or alternatively, and antegrade spread from the gasserian ganglion to the nerve branches in the infratemporal and pterygopalatine fossae can then occur. Achievement of negative surgical margins in such cases is difficult.[75] Perhaps this is one of

the reasons why ACC of the SNT has the worst prognosis of all sites in the head and neck.[137,138] The mechanism of perineural spread of cancer is poorly understood. Neural cell adhesion molecules (NCAMs) may have a role in the pathogenesis of perineural spread of malignant tumors including ACC and SCC.[32,33]

Lymphatic spread of ACC is uncommon. The incidence of lymph node metastasis from ACC detected at presentation or developing later in the course of the disease ranges from 10% to 30%.[139] Metastasis to the regional lymphatics is more common in tumors originating from the oral cavity (37%) than the parotid gland (19%). The rate of occult metastasis in patients undergoing elective neck dissection for the clinically negative neck is 17%, and the role of elective neck dissection remains unclear.[140,141] The development of lymph node metastasis was associated with poor outcome despite aggressive therapy.

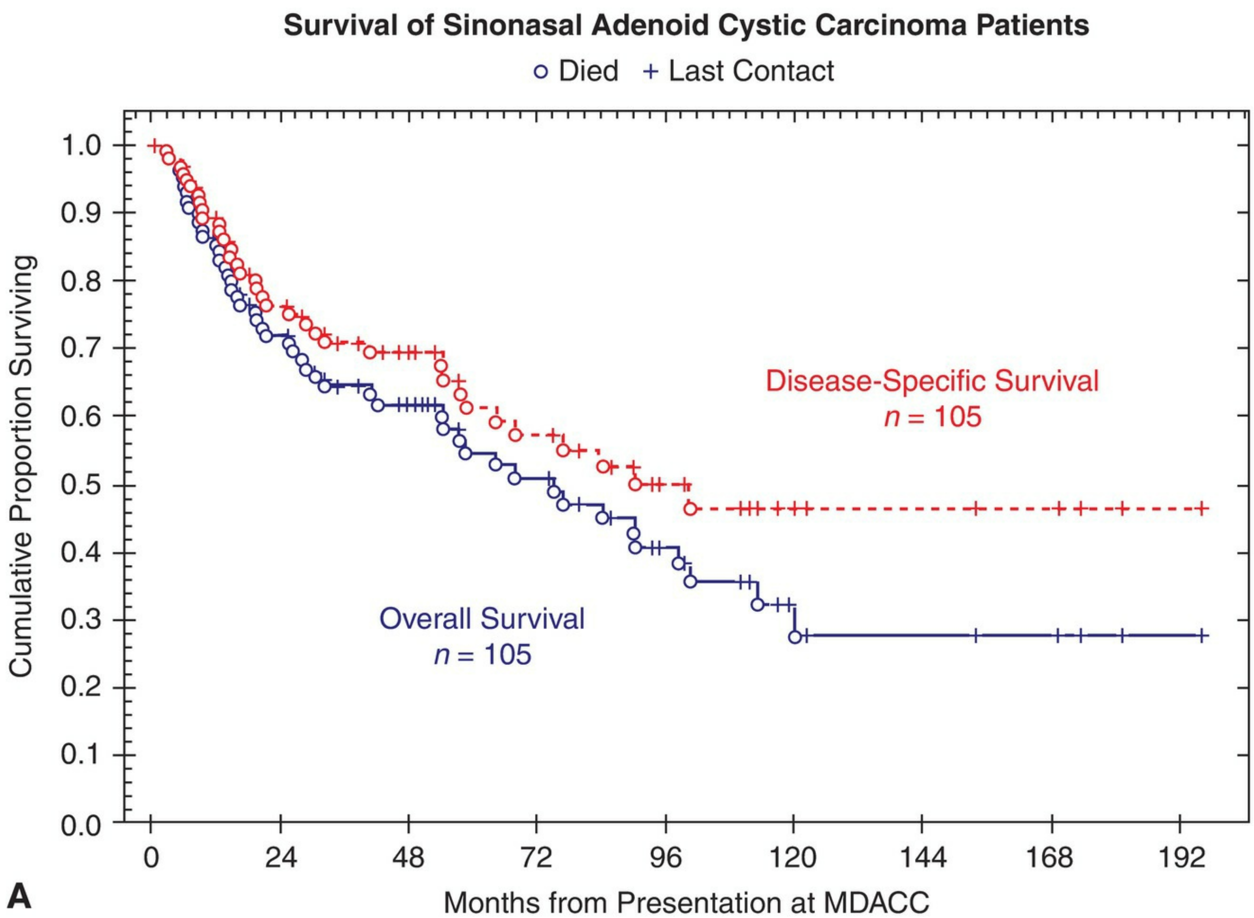
Distant hematogenous dissemination is common cause of treatment failure in patients with ACC. In a recent international retrospective review of 489 patients with ACC of the head and neck treated between 1985 and 2011 in nine cancer centers worldwide, 111 patients (22%) developed distant metastases during follow-up.[138] Twenty-nine of them (26%) also had locoregional failure, whereas distant disease was the only site of recurrence in the remaining 82 patients (74%). The most common site of distant metastases was the lung (20%), followed by bone (4%), liver (3%), and brain (1%). Median interval to the diagnosis of distant metastasis was 30 months (range, 2 to 192 months). Multivariate analysis revealed that age ≥70 years, primary site, orbital invasion, and N classification were independent predictors of distant metastases. Most importantly, the metastasis site had a significant impact on both overall (p = 0.04) and disease-specific (p = 0.03) survival. Analysis of outcome according to the site of distant metastasis showed that patients with bone and brain metastases had the poorest outcome, with 31% and 25% median survival, respectively. In contrast, patients with lung and liver metastases had significantly better survival, with 66% and 84% median survival, respectively (p = 0.04).

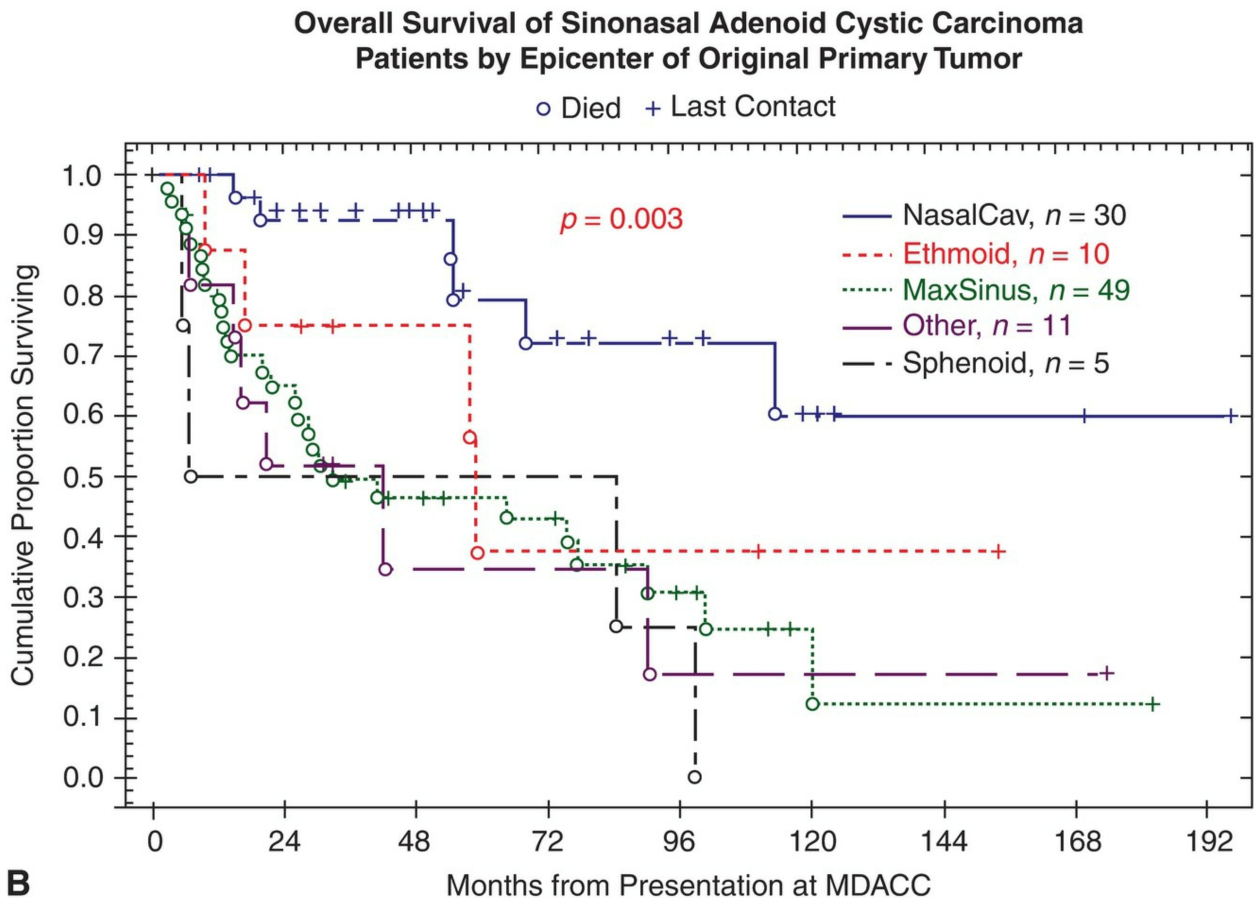
ACC is an indolent cancer, and late recurrences are common. Survival continues to decline well beyond 5 years and up to 20 years after treatment. Therefore, evaluation of reported outcomes of treatment should carefully examine the length of follow-up. A meta-analysis of sinonasal ACC

demonstrated a 1-year survival probability with treatment of 95%, a 5-year survival probability of 63%, and a 10-year survival probability of 32%.[133] This highlights the importance of lifelong follow-up and cancer surveillance for patients treated for sinonasal ACC.

Although surgery remains to be the mainstay of treatment of sinonasal ACC, multimodality treatment is warranted for the majority of sinonasal ACC. Surgery followed by postoperative radiation therapy is the standard treatment approach[25,142] and has been shown to provide the better survival outcomes than single-modality therapy.[25,143,144] A recent systematic review of studies for sinonasal ACC from 1960 to 2012 demonstrated that surgery with postoperative radiotherapy is the most commonly used and may possibly be the most effective therapy, and aggregate patient data meta-analysis revealed a 5-year survival rate of 62.5%.[133] The largest single institution experience of patients with sinonasal ACC was published by MDACC in 2007 and reported similar findings.[25] Of the 105 consecutive patients reviewed, the majority of patients presented with T3/T4 (77%), N0 (98%), and M0 (97%) disease. Surgery was the initial therapy in 70% of patients and the majority (85%) of patients treated with surgery received postoperative radiation therapy. The mean follow-up after the end of original treatment to the date of last contact was 76.6 months. Surgery with postoperative adjuvant radiation provided the best overall and DSS compared with other treatment modalities ($p = 0.018$ and $p = 0.05$, respectively). The local recurrence rate was 30%, and the distant metastases rate was 38%. The 5-year OS and DSS rates were 63% and 71%, respectively[25] (**Fig. 10.52A**). When the OS and DSS of patients were compared according to the epicenter of the original tumor, patients with nasal cavity tumors had the best survival, and patients with sphenoid tumors had the worst survival ($p = 0.003$ and $p = 0.031$, respectively) (**Fig. 10.52B**). Skull base invasion also was identified as a significant factor for overall and DSS compared with no skull base invasion ($p = 0.029$ and $p = 0.031$, respectively). Patients with stage IV disease had worse OS than patients with stage I, II, and III disease ($p = 0.018$) (**Fig. 10.52C**). In addition, when patients were grouped according to T classification, patients who had T4 disease had a worse OS compared with patients who had T1, T2, or T3 disease ($p = 0.013$). When the histopathologic types of ACC were compared, there was a significant difference in overall and DSS. Patients with cribriform tumors had the best survival, and patients

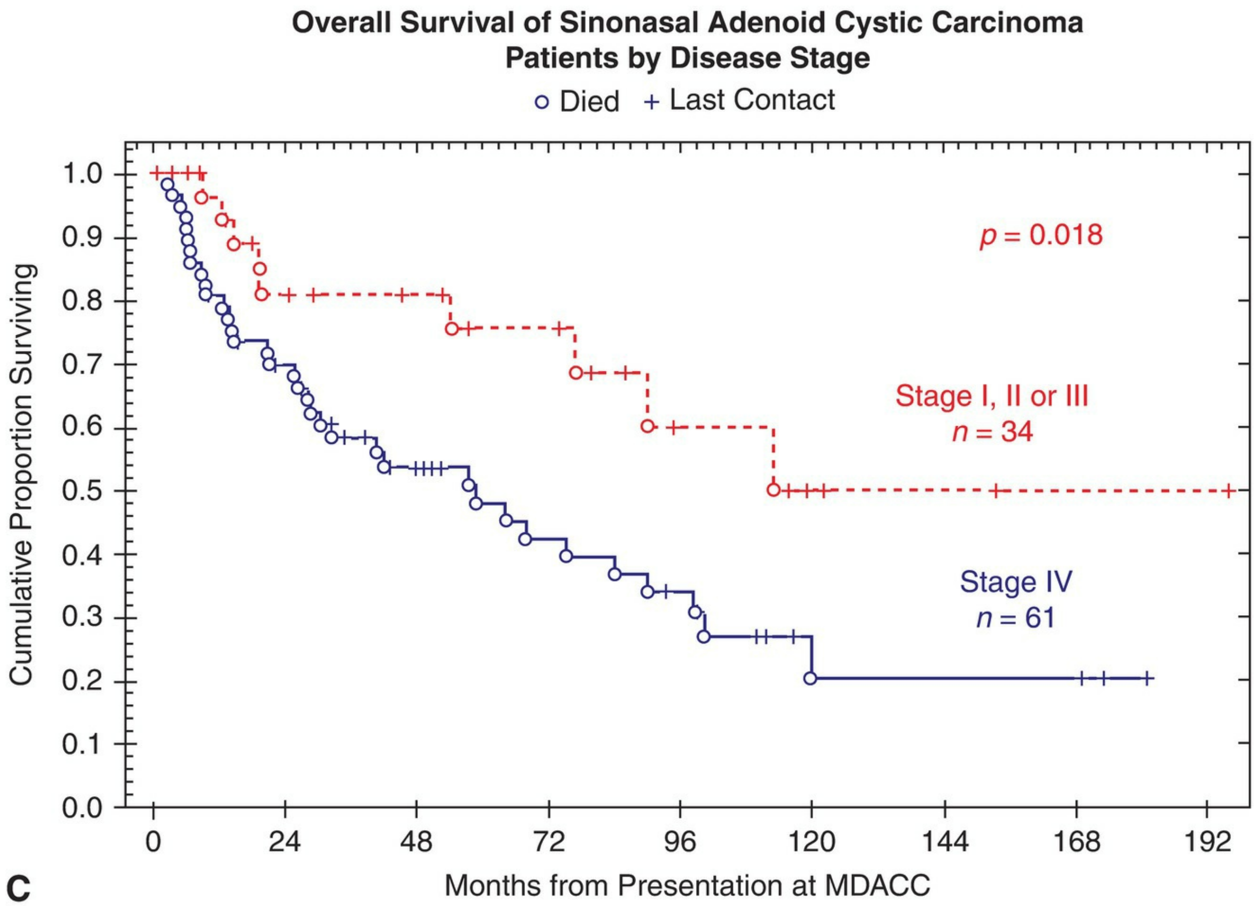
with solid tumors had the worst outcome ($p = 0.002$ and $p = 0.019$, respectively) (**Fig. 10.52D**).[25]





Overall Survival of Sinonasal Adenoid Cystic Carcinoma
Patients by Epicenter of Original Primary Tumor
Died
Last Contact
p = 0.003
NasalCav, n = 30
Ethmoid, n = 10
MaxSinus, n = 49
Other, n = 11
Sphenoid, n = 5
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
168
192
Months from Presentation at MDACC

B



Overall Survival of Sinonasal Adenoid Cystic Carcinoma
Patients by Disease Stage
Died
Last Contact
p = 0.018
Stage I, II or III
n = 34
Stage IV
n = 61
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
168
192
Months from Presentation at MDACC

C

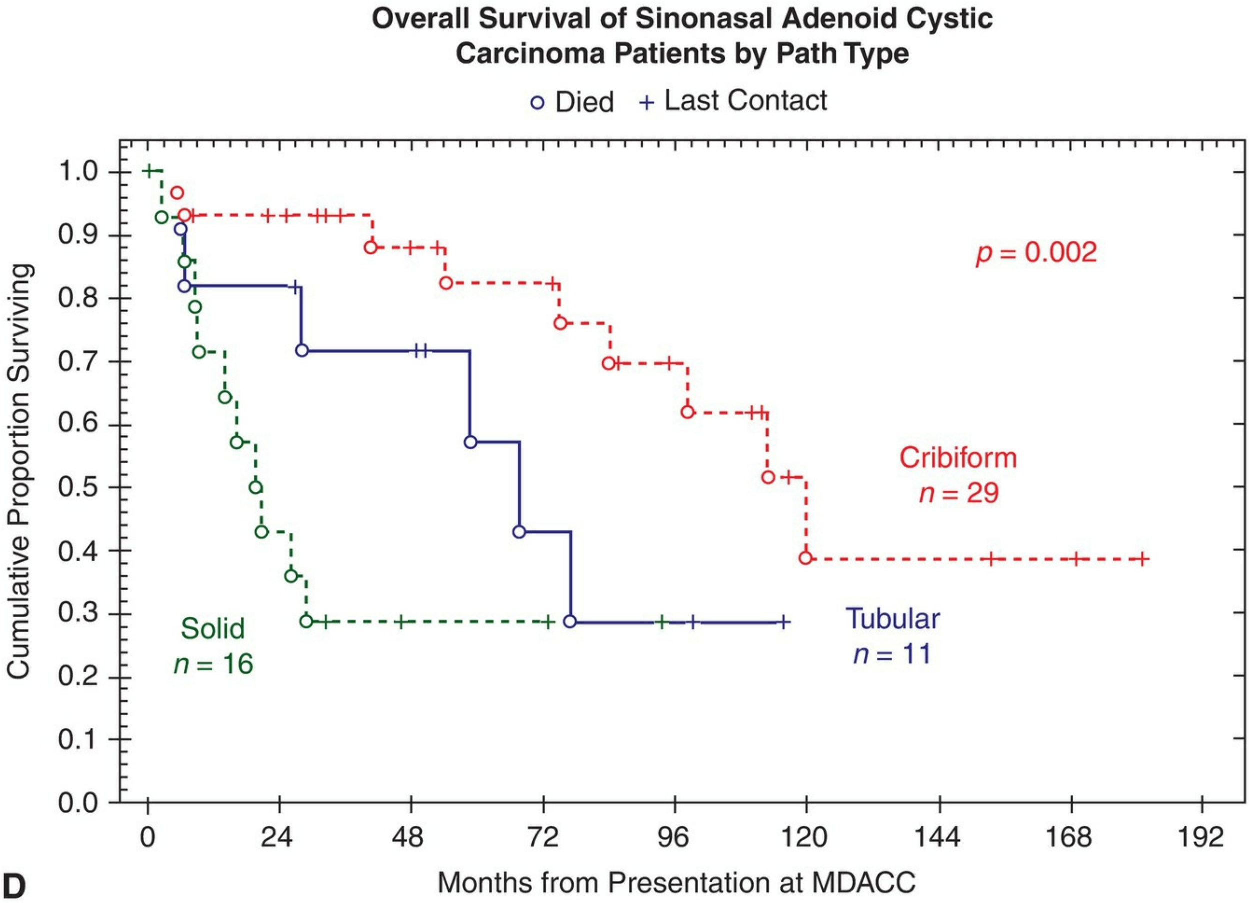


Figure 10.52. A–D: Survival of patients with ACC.

Several studies suggested that fast-neutron radiation therapy provides higher rates of locoregional control of unresectable or recurrent ACC compared to photon or electron radiation therapy and perhaps should be considered the initial treatment of choice in some cases.[145–147] In one study of patients treated with fast neutron for gross inoperable, residual unresectable, or recurrent disease, the 5-year locoregional control rates were 92% for patients treated definitively (without a prior surgical procedure), 63% for those treated postoperatively for gross residual disease, and 51% for those treated for recurrent disease after a surgical procedure.[148] This study suggested that neutron irradiation alone may be the therapy of choice in the treatment of some patients with unresectable advanced stage ACC and that surgery should be limited to those patients in whom disease-free margins can be obtained. The potential morbidity of a “debulking” surgical procedure before neutron irradiation is not warranted because no improvement in locoregional control can be demonstrated over that achievable with neutron

therapy alone.

A study of 75 patients with inoperable, recurrent, or incompletely resected ACC showed that fast-neutron radiotherapy provides higher local control rates than a mixed beam and photons. This advantage for neutrons in local control however was not transferred to significant differences in survival because of a high incidence of distant metastasis, which occurred in 40% of these patients.[146] In another recent study of 72 patients with recurrent or gross residual ACC after surgery treated with fast-neutron therapy, the RFS was 83% after 1 year, 71% after 2 years, and 45% after 5 years.[147] These impressive results are encouraging; however, the use of fast-neutron radiation therapy is hampered by the lack of its widespread availability. Currently, only a few facilities are equipped with the technology and expertise of delivering fast-neutron radiation therapy.

More recently, proton therapy has been reported to have promising initial outcomes for the treatment of advanced unresectable or recurrent ACC of the head and neck.[149] In a study of 23 patients with ACC of the skull base by Pommier et al.[150] from the Mass Eye and Ear Hospital, the 5-year overall and DSS were 56% and 77%, respectively. Twelve patients had been treated with prior surgery with gross residual disease or positive resection margins. At 5 years, the local control was 93%, and the freedom from distant metastasis was 62%. The development of multifield optimization (MFO) through intensity-modulated proton therapy (IMPT) may further enhance the efficacy of proton therapy for patients with head and neck tumors. Frank et al.[151] from MDACC reported the first clinical report of MFO-IMPT for head and neck tumors. Early clinical outcomes are encouraging and warrant further investigation of proton therapy in prospective clinical trials.

Another emerging approach in treating unresectable ACC is the use of concurrent chemoradiation. In a recent report of 16 patients with unresectable head and neck ACC treated with concurrent chemoradiation, 13 patients were alive and 7 without signs of disease with a median follow-up of 61 months.[152] Tumor progression was noted in eight patients (50%) (distant metastasis in five patients and local tumor progression in three patients) with a median time to progression of 25 months (range, 4 to 52 months). OS, PFS, and LPFS rates at 5 years were 87%, 39%, and 61%, respectively. This study suggested that concurrent chemoradiation is a feasible treatment option and may lead to sustained locoregional tumor control in patients with nonresected

ACC of the head and neck.

Systemic therapy including chemotherapy and targeted therapy is generally reserved for the palliative treatment of symptomatic locally recurrent or metastatic disease that is not amenable to further surgery or radiation.[153,154] Prospective trials of chemotherapy in advanced ACC are limited, and the optimum regimen is unclear. A recent systematic review summarized and rated the quality of trials assessing chemotherapy for treatment of ACC. Endpoints evaluated include tumor response and rates of symptomatic improvement in 34 trials involving 441 patients.[155] Single-agent mitoxantrone, cisplatin, epirubicin, vinorelbine, paclitaxel, and gemcitabine were studied in 141 patients. Objective major responses were uncommon (18 of 141), with none observed in the 14 patients who received paclitaxel or the 21 patients who received gemcitabine. No responses were seen in previously treated patients. Reported response durations ranged from 5 to 20 months. Stable disease was more common than objective responses and was reported in 64 of 111 patients. Disease stabilization might be a marker of antitumor activity, but this is difficult to interpret unless clear evidence of progression is documented before the start of therapy. Notable rates of disease stabilization (in 39 of 66 patients) were also seen in trials that required progressive or symptomatic disease for study entry.[155]

The activity of standard cytotoxic drugs given in combination was studied in 143 patients enrolled in 17 trials.[155] Less than 15% of patients had prior systemic therapy. By contrast with single-agent studies, most patients had distant metastases. Cisplatin and doxorubicin were the most common drugs given in combination regimens and were given with cyclophosphamide (CAP regimen) in four trials. Although the trials assessing CAP regimen used slightly different doses and schedules, major objective responses were noted in nine of 36 patients (response rate 25%; 95% CI, 11% to 39%). Regimens containing both cisplatin and an anthracycline other than doxorubicin also showed modest activity, as did other platinum-based regimens. In 14 studies, cisplatin-based regimens led to objective responses in 29 of 118 patients (response rate 25%, 17% to 33%). Response duration ranged widely, from 6 to 77 months. Experience with carboplatin-based regimens has been even more limited: a study of carboplatin plus paclitaxel reported a response rate of 20% (2 of 10 patients), and two studies reported that all seven patients who received carboplatin instead of planned cisplatin did not respond to therapy.

Disease stabilization in patients who had been progressing was reported in trials of cisplatin-based therapy. Duration of disease stabilization for patients with ACC given any regimen was reported in only two trials. In two studies, none of the previously treated patients responded to trial therapy.[155]

Because chemotherapy has been of only limited palliative benefit in patients with advanced disease, and there has been little exploration of its use in definitive management, recent investigation has focused on identification of the characteristic molecular signatures and genomic alterations in ACC and other SG cancers.[153] These efforts have suggested the potential for molecularly targeted therapies, and clinical trials exploring this approach are currently underway.[154] A good example is the imatinib experience in c-kit–positive ACC. High expression of c-kit has been noted in up to 90% of ACC tumors. In a systematic review by Laurie et al.,[155] six studies have assessed imatinib activity in ACC, with only two objective responses reported in 71 evaluable patients. Both responses were stable (durations of 14 months and at least 15 months) and occurred in the only study that required high c-kit expression and progressive disease for study entry. Stable disease was reported more commonly than objective responses; however, evidence of disease progression at study entry was either not required or not stated in most trials. One trial did explore the efficacy of imatinib in combination with cisplatin: patients received imatinib alone for 2 months, and those who did not respond or progressed were also given cisplatin. Of 17 evaluable patients, 2 patients progressed, and no objective responses were observed during the imatinib-alone phase. With the addition of cisplatin, three partial responses were noted. Studies of other targeted agents in ACC are summarized in the meta-analysis by Laurie et al.[155] Phase 2 studies of the EGFR inhibitors gefitinib (19 patients) and cetuximab (23 patients) did not report any major objective responses. Disease stabilization was reported with both drugs; however, not all patients had progressive disease at the time of study entry. Lapatinib, a dual inhibitor of EGFR and HER2 (also called ERBB2), was studied in 19 patients who had documented radiologic progression, symptomatic deterioration, or both, within 6 months of study entry. Immunohistochemistry evidence of expression of either target was required. No objective responses were seen, although nine patients (47%) had disease stabilization for at least 6 months. The proteasome inhibitor bortezomib has been studied in 25 patients. Eligible patients had evidence of disease

progression within the previous 9 months. Bortezomib was given until disease progression, at which time doxorubicin was added, given weekly for 2 of 3 weeks. No objective responses were reported with single-agent bortezomib, but 17 patients had disease stabilization, with a median PFS of 8.5 months. One objective response was seen with the addition of doxorubicin. Overall, therapy was well tolerated. In summary, recent progress in our understanding of the molecular biology of ACC promises the possibility that more specific targeted therapies might prove useful. The careful design and conduct of prospective clinical trials will be critical to improving our treatments for this disease.[153,154]

Mucoepidermoid Carcinoma.

MEC is the most common SG malignancy. Primary sinonasal MEC (SN-MEC) is rare. It is most commonly located in the nasal cavity, followed by the maxillary sinus. There are few published studies reporting on the natural history of MEC.[156–158] In 2015, a report of the SEER database (1973 to 2010) identified 149 cases of SN-MEC and 4,234 cases of SG-MEC.[159] They analyzed the demographic, clinicopathologic, and survival characteristics of SN-MEC and established comparisons with primary major SG-MEC. Mean ± standard deviation (SD) age at diagnosis for SN-MEC was 58.6 ± 16.6 years. High histologic grade (i.e., grades 3 and 4) at the time of diagnosis was more common among SN-MEC than SG-MEC (42.3% vs. 25.5%, $p < 0.0001$). Overall 5-year DSS was 62% for SN-MEC and 84% for SG-MEC ($p < 0.001$). For SN-MEC, factors associated with poor prognosis were age [75+ years; hazard ratio (HR), 3.38; 95% CI, 1.25 to 9.51], higher tumor grade (grades 3 and 4; HR, 3.62; 95% CI, 1.75 to 8.22), larger tumor size (>4 cm; HR, 8.36, 95% CI, 1.59 to 153.74), and primary tumor site (ethmoid sinus; HR, 2.95; 95% CI, 1.28 to 6.23) (all $p < 0.05$). Survival was better among those treated with surgery [with (64.4% survival) or without (81.3% survival) adjuvant radiation therapy] than those treated with primary radiation therapy alone (25.6% survival) ($p < 0.05$). This report represents the largest series of SN-MEC to date and highlighted that although SN-MEC and SG-MEC share a common histology, there are important clinical differences between the two conditions.[159]

Esthesioneuroblastoma.

First described by Berger, Luc, and Richard in 1924, ENB, also known as

olfactory neuroblastoma, is a tumor of neural crest origin. It arises almost exclusively from the olfactory epithelium of the nasal cavity and paranasal sinuses. ENB represents 3% to 6% of all sinonasal cancers.[160]

Patients presenting with ENB are typically reported to have a slight male predominance and a bimodal age distribution, with one peak in the second decade of life and the second peak in the sixth decade of life.[161] However, a recent report from MDACC of 70 patients with ENB treated from 1992 to 2006, the median age at diagnosis was 51 years with a range 9 to 78 years.[162] The most common age group of presentation was the sixth decade (20%), followed by the fifth and seventh decades of life. This observation is confirmed by a population-based analysis of the SEER database, where patients in the second decade of life comprised <10% of the cohort.[163]

The most common site of origin is in the superior nasal vault in the region of the cribriform plate.[160,164] “Ectopic” origin in lower nasal cavity or within one of the paranasal sinuses (e.g., maxillary sinus) may occur.[160,164] ENB may on occasion present as an intracranial (frontal lobe) mass with involvement of the superior aspect of the cribriform plate or rarely occur intracranially with no intranasal component.[165]

Microscopically, the tumor is composed of round cells larger than lymphocytes, with round nuclei, dense chromatin, and inconspicuous cytoplasm. The hallmark of this tumor is the arrangement of these cells into rosettes, pseudorosettes, or sheets and clusters. In the absence of rosettes and pseudorosettes, the differential diagnosis includes peripheral neuroectodermal tumor (PNET), anaplastic carcinoma, malignant lymphoma, malignant melanoma, plasmacytoma, embryonal rhabdomyosarcoma, and metastatic small cell carcinoma (SmCC). ENB can be particularly confused histologically with several other “small blue round cell tumors” of the nasal cavity and paranasal sinuses, including SNUC, NEC, SmCC, pituitary adenoma, melanoma, lymphoma, and rhabdomyosarcoma. Expert histopathologic review is essential in confirming the diagnosis because a study demonstrated a significantly high misdiagnosis rate of patients referred to MDACC with presumed diagnosis of ENB.[43] Immunohistochemistry is usually needed to establish the diagnosis in such cases, and ENB usually expresses a variety of neuroendocrine markers such as neuron-specific enolase (NSE), chromogranin, and synaptophysin but usually does not

express cytokeratin.[42]

The distinction between ENB, NEC, SNUC, and SmCC is critical because it has a huge impact on the choice of initial therapy and prognosis. In 2004, Rosenthal et al.[23] reported the outcomes of 72 adults with pathologically proven, nonmetastatic, primary sinonasal neuroendocrine tumors treated at MDACC from 1982 to 2002. There were 31 patients with ENB, 16 patients with SNUC, 18 patients with NEC, and 7 patients with SmCC. Patients with ENB usually were treated with local therapy alone (surgery and/or radiotherapy); only 3 of 31 patients (9.7%) received treatment (radiation) to regional lymphatics, and only 5 of 31 patients (16.1%) received chemotherapy. In contrast, patients with non-ENB histologies usually received chemotherapy (10 of 16 patients with SNUC, 12 of 18 patients with NEC, and 5 of 7 patients with SmCC), and nonsurgical locoregional therapy was used more frequently (6 of 16 patients with SNUC, 4 of 18 patients with NEC, and 5 of 7 patients with SmCC). The median follow-up for surviving patients was 81.5 months (range, 6 to 266 months). OS and local, regional, and distant disease control at 5 years was best for ENB and declined significantly for NEC, SNUC, and SmCC in descending order (**Table 10.7**). Delayed regional lymph node metastasis was common in ENB and increased the regional failure rate from 8.7% at 5 years to 31.9% at 10 years.[23]

Table 10.7 Summary: Survival and Patterns of Failure in Patients with Sinonasal Carcinomas with Neuroendocrine Differentiation

Histology	5-Year Rates (%)			
	OS	LC	RF	DM
ENB	93.1	96.2	8.7	0.0
NEC	64.2	72.6	12.9	12.3
SNUC	62.5	78.6	15.6	25.4
SmCC	28.6	66.7	44.4	75.0

Rosenthal DI, et al. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. *Cancer.* 2004;101(11):2567–2573.

The prognosis of ENB depends on the extent of disease at presentation. Several staging systems have been proposed, and no single one has become universally accepted. Kadish staging was the first classification system for ENB. Although it was initially described based on 17 patients only, it remains the most popular and simplified go-to staging system.[166] Its main limitation is that it only assesses local disease extent: Kadish A for tumors limited to the nasal cavity only, Kadish B for involvement of the paranasal sinuses, and Kadish C for extension outside the paranasal sinuses. Dulguerov[167] and Biller[168] then proposed more detailed TNM-type staging systems. Dulgerov's classification differentiates between intracranial and/or orbital extension, whereas Billers' separates resectable versus nonresectable parenchymal brain disease. More importantly, both of these staging systems take into account regional neck node involvement and distant metastasis. Lymph node metastasis was in fact shown to be in itself a major determinant of prognosis and to be associated with poorer outcome. In the Princess Margaret report, Dulguerov classification correlated most closely to survival and recurrence.[169] Zafereo et al.[170] also demonstrated that the TNM-based systems (Dulgerov and Biller) in contrast to Kadish staging could reliably identify worse DFS. Therefore, recognizing the poor prognostic implications of regional and distant disease, Morita and his colleagues[171] from the Mayo Clinic proposed a more accurate and practical modification to the Kadish system. Cervical lymphadenopathy and distant metastasis are incorporated as a fourth "D" category. In this scheme, Jethanamest et al.[163] in a SEER database review showed significant outcome differences among the four groups with a worse DFS for the D category. ENB has its own T and N designation in the most recent staging of Sinonasal Cancer According to the AJCC 7th edition that was modified in 2010 (Table 10.2). This staging system, which relies on high-resolution imaging prior to therapy, recognizes the early involvement of the cribriform plate, but it allows for tumors that arise below the cribriform plate and that can be treated in a more conservative fashion to be staged separately. Also, a stage is included at which a tumor is intracranial but remains extradural and is therefore likely to have a better prognosis than a tumor that has invaded the brain. Nodal disease in this classification is either absent (N0) or present (N1). Despite the efforts to better characterize ENB's clinical behavior, staging systems individually are far from ideal. Although some have used them as predictors of outcome, they remain, for many, questionable and suboptimal tools of stratification for

patients with ENB.[172]

There is evidence that the histologic grade of ENB influences biologic behavior, particularly as it relates to disease progression, local recurrence, and metastasis. Histologically, well-differentiated ENB forms nests or sheets of cells in a neurofibrillary stroma. Nuclei are small, round to ovoid with punctuate “salt and pepper” chromatin. The glandular architecture with true lumen rosette (Flexner-Wintersteiner) or pseudorosette (Homer-Wright) formations is characteristic.[172] The Hyams grading system, proposed back in the late 80s by the American Forces Institute of Pathology, is a scheme that captures the spectrum of ENB maturation, from indolent disease to more aggressive behavior.[173] A score from 1 to 4 is given based on the degree of expression of key adverse features: mitotic activity, nuclear pleomorphism, rosette formations, necrosis, disorganized architecture, and sparse fibrillary matrix (**Fig. 10.53**).

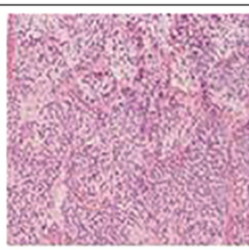
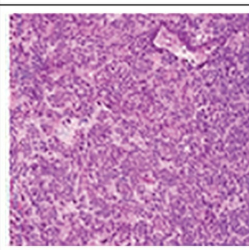
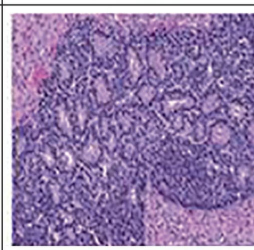
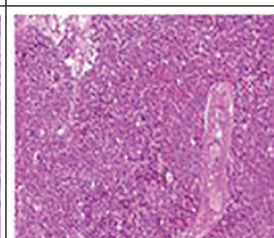
HYAM’s	Grade 1	Grade 2	Grade 3	Grade 4
Architecture	Lobular	Lobular	Variable	Variable
Mitotic Activity	Absent	Present	Prominent	Marked
Nuclear Pleomorphism	Absent	Moderate	Prominent	Marked
Fibrillary Matrix	Prominent	Present	Minimal	Absent
Rosette	HW	HW	FW	FW
Necrosis	Absent	Absent	+/– Present	Common
Hematoxylin & Eosin				

Figure 10.53. Key features and criteria for HYAM’s grades 1, 2, 3, and 4 and their corresponding histopathologic H&E slides.

Although the initial data supporting the value of the Hyams classification for prognostication has been critically received because of the subjective nature of the grading, a building body of evidence is trending toward validation of grade as an essential tool in prognostication and management. Three recent studies from the Mayo Clinic,[174] UCSF,[175] and The Institue Gustave Roussy in France[175] demonstrated that the Hyams grading system in

either an independent or a complimentary predictor of outcome and prognosis compared to the Kadish or AJCC staging systems. Bell et al.[173] from MDACC published the most recent and largest study comparing the effect of grade and stage on prognosis. Out of 124 ENB cases identified, 121 were assessed for Hyams grading and 109 for modified Kadish staging. Clinically, of the 109 cases that had been staged, 16% were stage A, 33% stage B, 43% stage C, and 8% stage D. Histologically, 62% of tumors were low grade (1/2), 21% were high grade (3/4), and 17% were metastasis. Although high-grade ENB had significantly worse DFS, the analysis revealed no statistically significant differences, for either modified Kadish stages or TNM stages, in terms of recurrence, distant metastasis, or 5-year survival rates. Briefly, in this large cohort of ENB, high grade was significantly associated with poor outcome, whereas advanced stage was not. The collective evidence of these studies suggests an important prognostic impact of histologic grade and perhaps the need for and intensity of adjuvant therapy in high-grade tumors.

Adequate surgical resection is the treatment of choice for olfactory neuroblastoma.[160] Early-stage, low-grade ENB, confined to the nasal cavity, may be treated with surgery alone provided resection margins are negative for tumor. For advanced disease and high-grade tumors, treatment involves multimodality therapy. In such cases, surgery combined with radiation is superior to surgery alone as definitive therapy.[163,165,176–179] In a recent study of 70 patients with ENB treated at MDACC, patients who were treated with surgery alone had a median DSS of 87.9 months, whereas those who were treated with surgery and postoperative radiation had a median DSS of 218.5 months ($p = 0.047$).[162] Radiation therapy followed by surgery may also be used. The University of Virginia group treats patients with Kadish A or B tumors with preoperative radiation therapy and those with Kadish C tumors with preoperative sequential chemotherapy and radiation therapy. The 5- and 15-year DFS were 86.5% and 82.6%, respectively. The local–regional recurrence was 24%, and distant recurrence was 10%.[180]

Several surgical approaches have been described. Whatever approach is used, the goal of surgery must be complete surgical resection with tumor-free margins. This offers the best chances of locoregional control as well as survival. Because the tumor originates from the olfactory epithelium, most tumors arise close to or within the nasal roof. In most cases, the cribriform plate will usually, by necessity, need to be resected en bloc with the tumor to

achieve adequate surgical margins. The most commonly used approach to adequately resect tumors in these locations is a combined anterior craniofacial resection. Over the past decade, endoscopic surgery has become an accepted treatment modality in early-stage ENB. Several small series have reported 3- to 5-year DFS of between 89% and 100%.[54,68,69,181–184] In a meta-analysis of 23 papers comparing endoscopic to open surgery, endoscopic surgery was most frequently used to treat Kadish A and B disease and resulted in a 10-year OS of 90%.[179] The incidence of local recurrence has been reported to be between 10% and 30%, and indications for postoperative radiation therapy or chemoradiation therapy include high Hyams grading, advanced stage disease, intracranial extension, and positive resection margins.[165,173,185,186]

Five to eight percent of patients will have neck disease at presentation and is a negative prognostic indicator.[165] These patients should be offered therapeutic nodal dissection with postoperative irradiation if indicated. Twenty-five percent of patients with untreated necks will develop nodal metastasis.[187] Delayed regional lymph node metastasis is common in ENB. In a study from MDACC, the regional failure rate was 8.7% at 5 years but rose to 31.9% at 10 years.[23] There are no reports that prophylactic neck dissection is beneficial, but there are limited data that ENI to the cervical nodal basin is associated with a reduction in relapse rates and should be considered in patient treated with advanced stage or high-grade disease.[188]

Despite promising 5-year outcomes, the results of long-term follow-up are not well reported. This is critical because recurrences continue to occur after 5 years. Ow et al.[160] from MDACC specifically reported long-term outcomes of ENB in a study with a median follow-up of 91.4 months (7.6 years). In their report, the median time to recurrence was 6.9 years, and the incidence of overall recurrence and distant metastasis (DM) was 46% and 15%, respectively. Recurrences have been reported beyond 10 years after the initial diagnosis, and patients treated for ENB warrant long-term follow-up.[49,180,189]

Sinonasal Undifferentiated Carcinoma.

The original definition for SNUC was reported by Frierson et al. as a “highly aggressive and clinicopathologically distinctive carcinoma of uncertain histogenesis with or without neuroendocrine differentiation but without

evidence of squamous or glandular differentiation” that typically presents with locally extensive disease.[190,191] SNUCs are rare tumors, with fewer than 200 reported cases. SNUCs can present from the third to ninth decade, with a median age in the sixth decade.[192] There is a slight male predominance.[192–194] The majority of SNUCs arise in the ethmoid and maxillary sinus.[194] Patients are symptomatic, presenting with nasal obstruction, epistaxis, proptosis, cranial nerve palsies, visual disturbances, or pain. Symptoms are of relatively short duration (from weeks to months) compared with other sinonasal neoplasms, which have a more gradual onset.[41] The majority of patients present with stage T4 disease,[194] and ~50% present with orbital involvement and/or skull base and brain involvement. The rate of lymph node metastasis is 10% to 30%, and distant metastasis occurs in 25% to 30% of patients, mostly to the lung and bone.[23,192–195]

The differential diagnosis of SNUC includes a variety of undifferentiated tumors that can be categorized as an epithelial or a nonepithelial neoplasm[41] (**Fig. 10.54**). Recently, we described a practical algorithm of immunophenotyping and genotyping for differentiating these neoplasms[41,42] (**Fig. 10.55**). A definitive diagnosis is important in making treatment recommendations that drive patient outcomes.

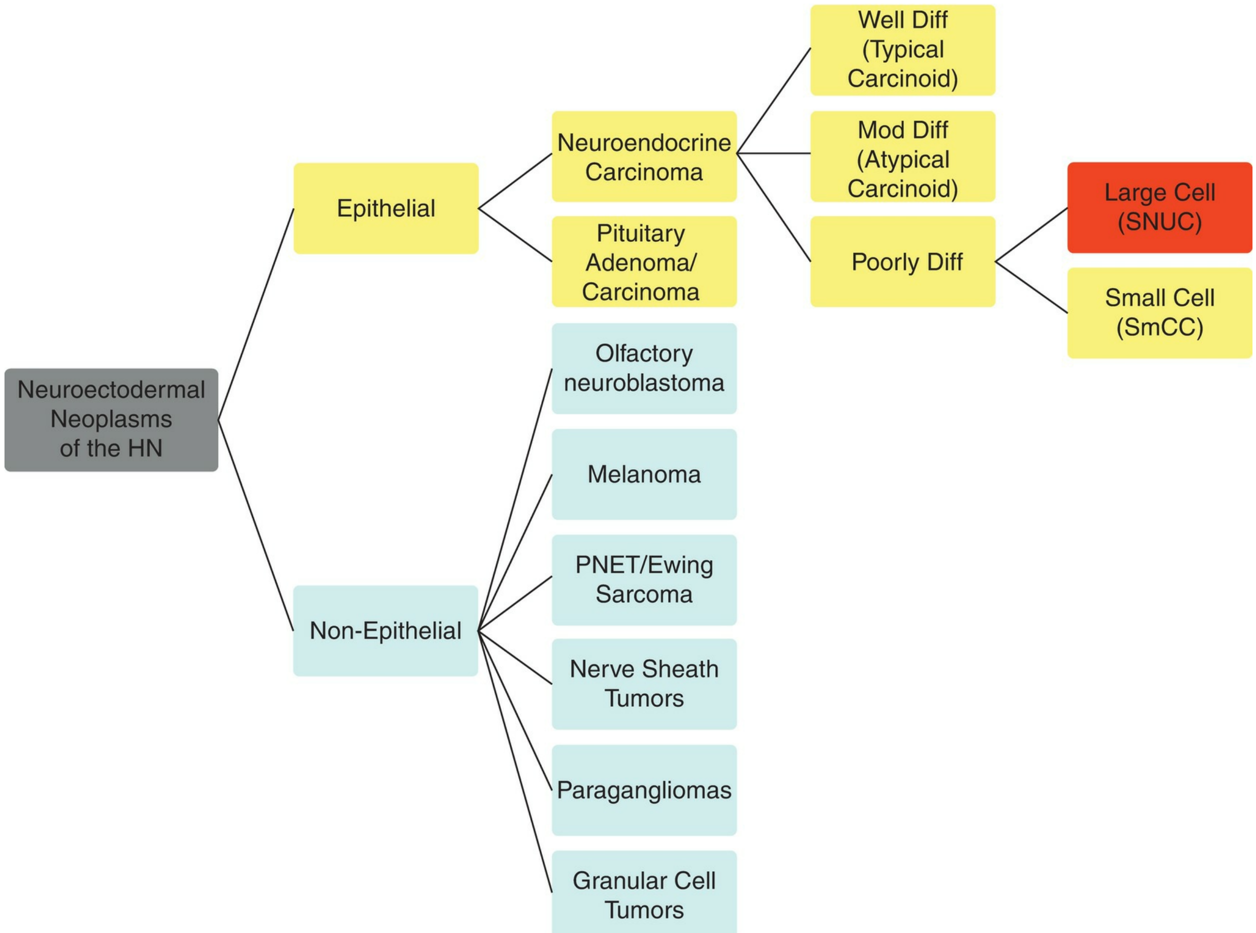


Figure 10.54. Neuroectodermal neoplasms of the head and neck.

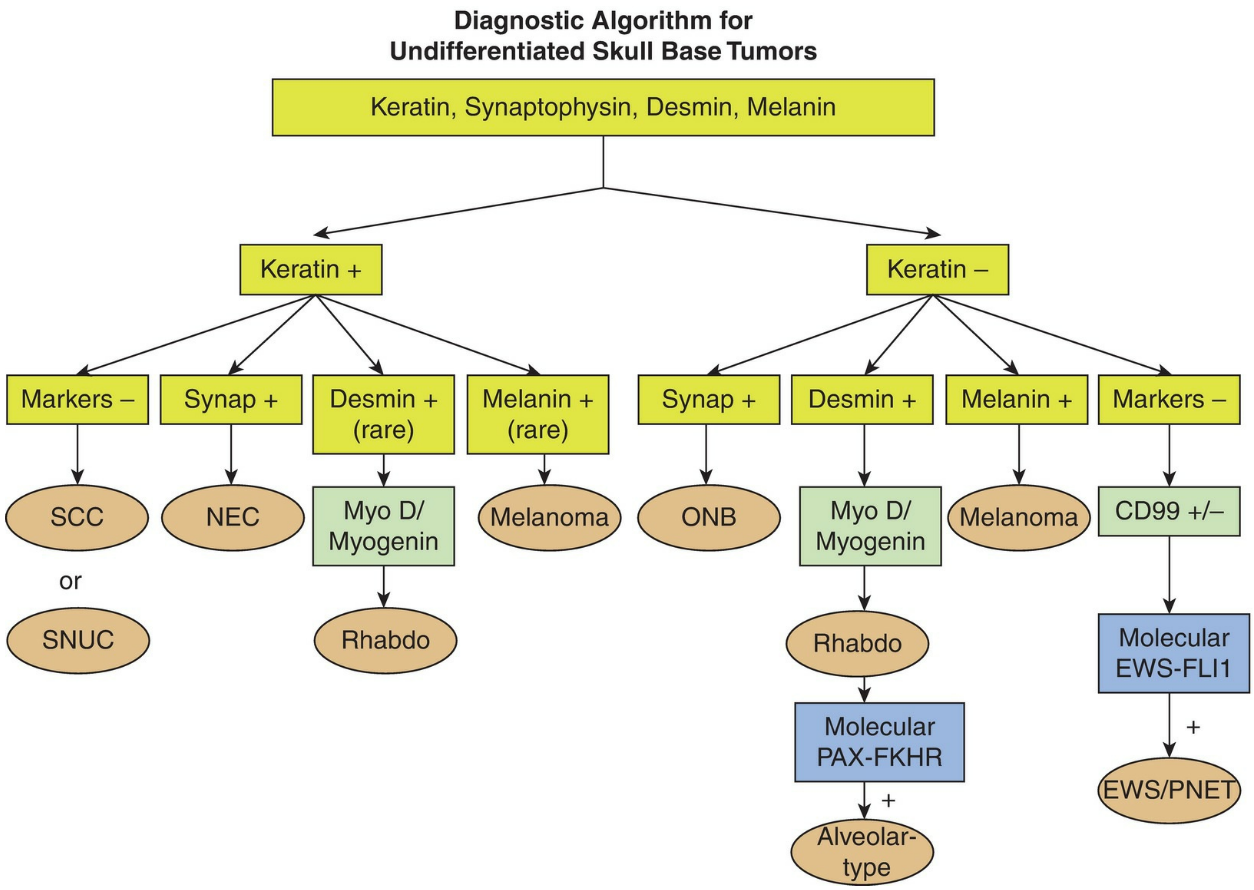


Figure 10.55. Diagnostic flow chart for immunohistochemical evaluation of poorly differentiated skull base tumors. An initial panel **(A)** of keratin, synaptophysin (Synap), desmin, and melanin markers allows for the classification of most neoplasms. Panel B includes confirmatory/ancillary markers and molecular studies for rhabdomyosarcoma (Rhabdo), MyoD or Myogenin, and PAX-FKHR for the alveolar type, and Ewing sarcoma/peripheral neuroectodermal tumor (EWS/PNET), CD99, and EWS-FLI1. ONB indicates olfactory neuroblastoma; NEC, neuroendocrine carcinoma; SCC, squamous carcinoma; SNUC, sinonasal undifferentiated carcinoma. (Cordes B, et al. Molecular and phenotypic analysis of poorly differentiated sinonasal neoplasms: an integrated approach for early diagnosis and classification. Hum Pathol. 2009;40(3):283–292, Ref. 42.)

The optimal treatment of SNUC is not well defined in the literature. The rarity of the disease combined with the inconsistent treatment strategies makes it difficult to draw any conclusions on the best treatment strategy for patients with SNUC. There is uniform adoption however of a multimodality approach given the advanced locoregional disease at presentation and the

propensity for distant dissemination.[23,192–204] In general, there are two major treatment strategies; the first is primary surgical resection followed by adjuvant radiation or chemoradiation, and the second is primary radiation or more often chemoradiation, with surgery reserved for salvage of persistent or recurrent disease. It is difficult to compare the outcomes of these two divergent strategies because the former (primary surgery) is more often reserved for "resectable" disease. This selection bias will preferentially include the less common but favorable disease for surgical treatment and assign patients with more advanced and less favorable disease to nonsurgical therapy. It is no surprise then that reported 5-year survival rates range from <10% to over 65%.[23,192–204]

Our preferred approach at MDACC for patients with SNUC is to start with induction or neoadjuvant chemotherapy. The rationale for this strategy is the relatively high risk of distant metastasis, which is a major component of treatment failure and death from disease. We treated 30 consecutive patients with this approach, and all but one patient had T4 (26 patients, 87%) or T3 (3 patients, 10%). The most common chemotherapy regimen used included platinum and etoposide. Response to chemotherapy was classified as complete in 4/30 (13%), partial in 14/30 (47%), stable in 6/30 (20%), and progressive disease in 6/30 (20%) of patients (**Fig. 10.56**). Patients with complete or partial response were more likely to receive chemoradiation (11/18, 61%) or radiation (5/18, 28%) than surgery (2/18, 11%) for their subsequent definitive locoregional therapy. By contrast, patients who showed no response to induction chemotherapy (stable or progressive disease) were more likely to receive surgery (8/11, 73%) than chemoradiation or radiation (4/11, 37%) for subsequent locoregional therapy. The survival outcomes of these 30 consecutive patients treated uniformly with this approach are shown in **Figure 10.57A**. These outcomes are better than those reported in the literature and may suggest an added advantage for incorporating neoadjuvant chemotherapy in the overall management of patients with SNUC. More importantly, response to chemotherapy was predictor of a more favorable survival regardless of subsequent locoregional therapy (**Fig. 10.57B**). We also continue to study the molecular characteristics of SNUC in an effort to either better predict response to therapy or provide novel targets for molecular therapy.[205] We were also able to establish and characterize a novel SNUC cell line in order to facilitate further research in the biology of this rare

disease.[206]

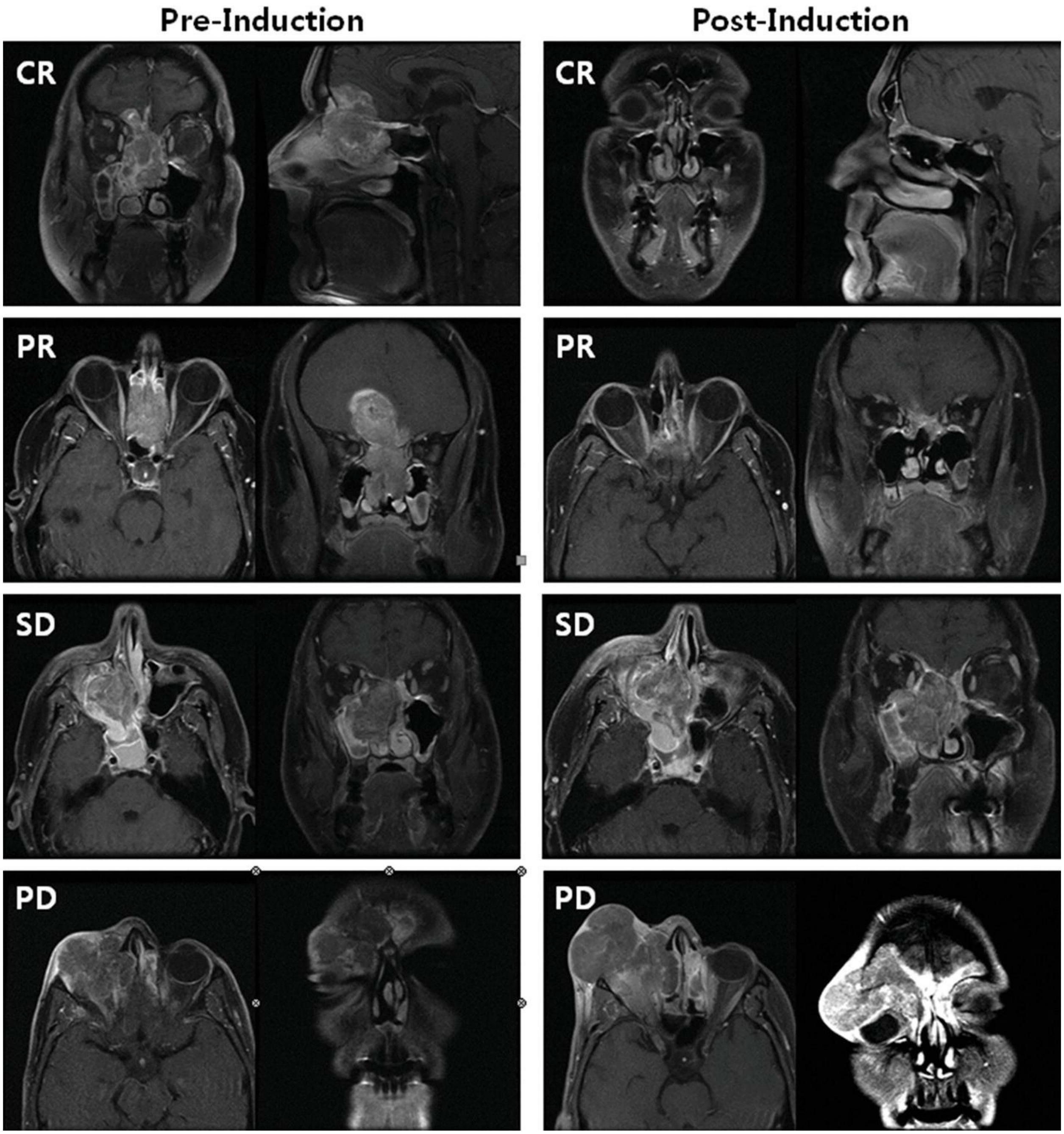
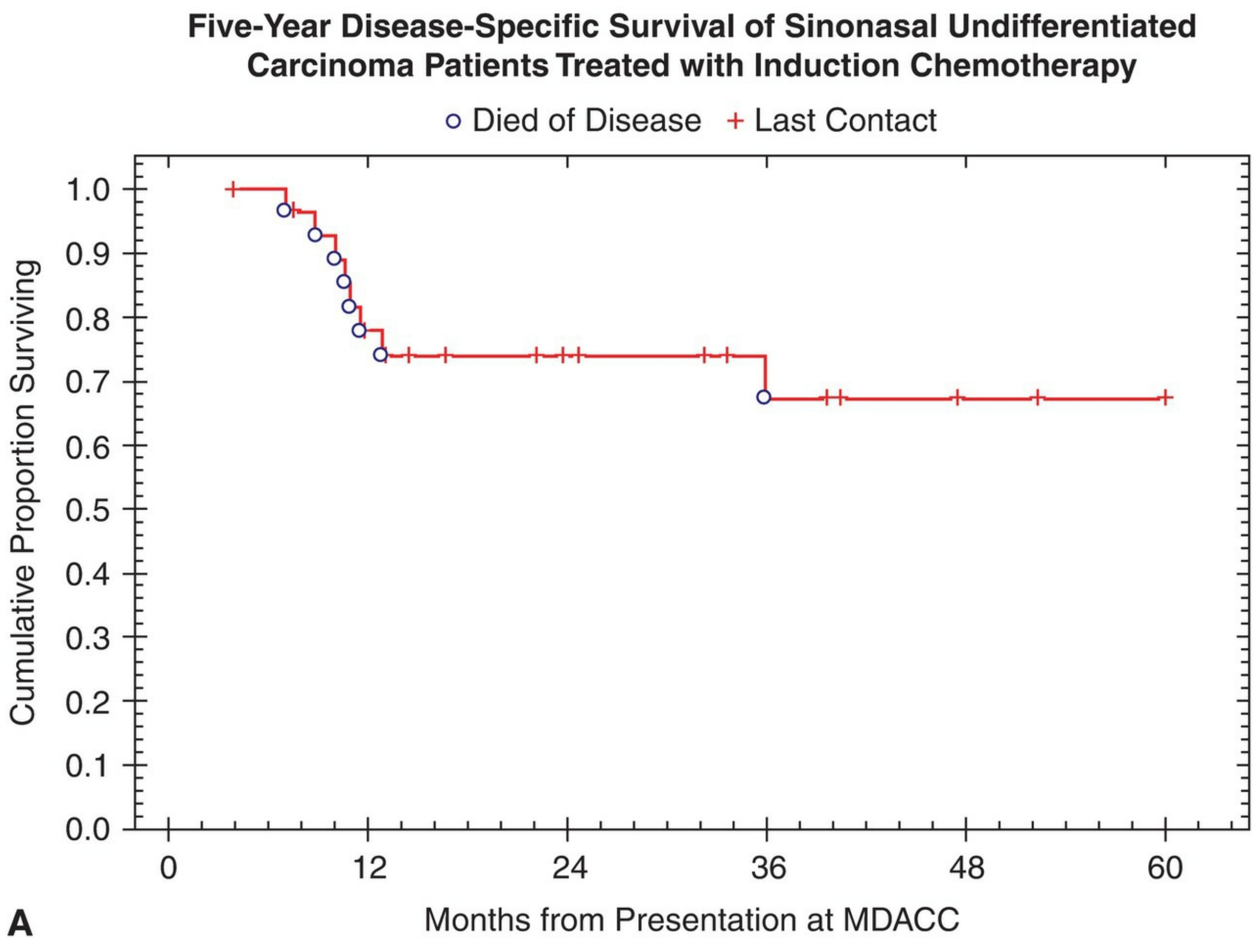
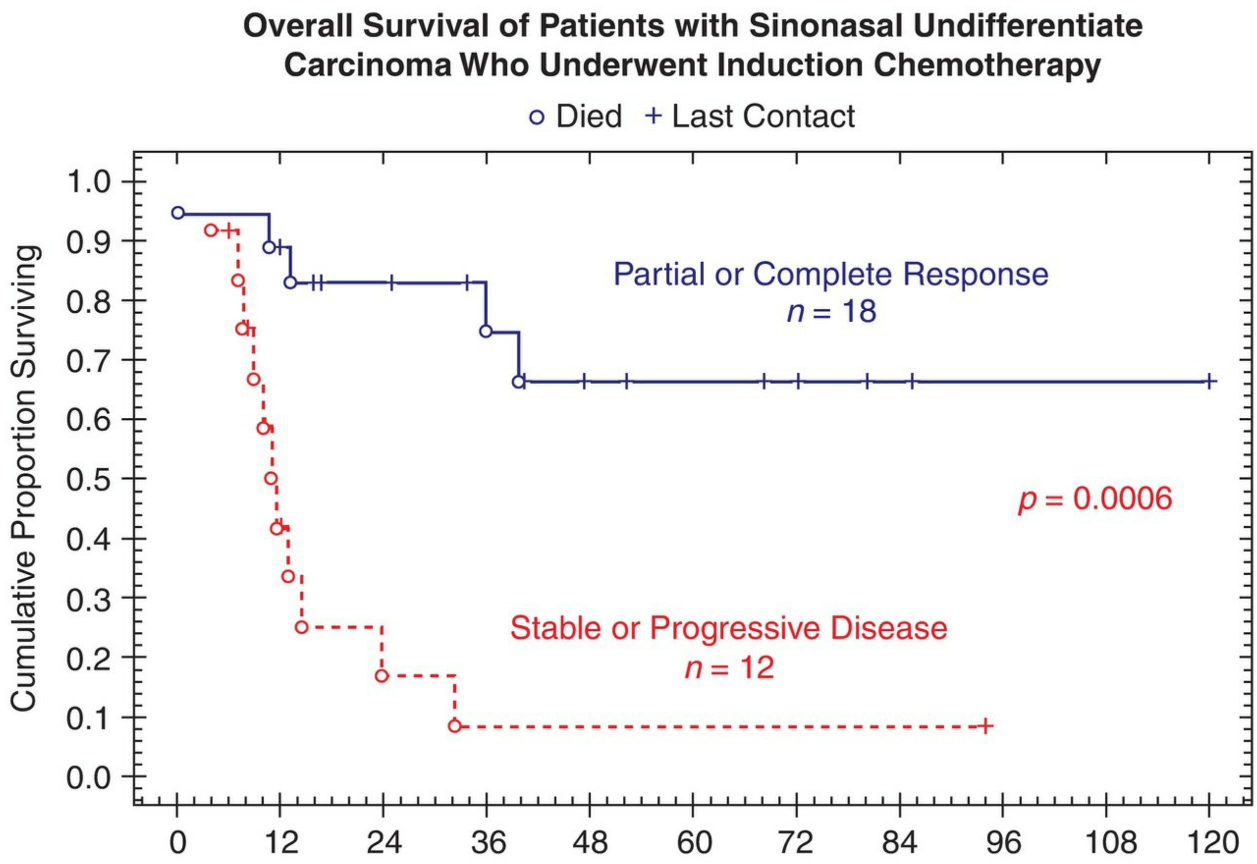


Figure 10.56. Response assessment to induction chemotherapy in patients with SNUC. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.


Five-Year Disease-Specific Survival of Sinonasal Undifferentiated Carcinoma Patients Treated with Induction Chemotherapy
Died of Disease
Last Contact
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
Months from Presentation at MDACC

A



B

Figure 10.57. Survival outcomes of patients with SNUC treated with induction chemotherapy at MDACC. **A:** Disease-specific survival. **B:** Overall survival stratified by response to induction chemotherapy.

Neuroendocrine Carcinoma.

NEC are very rare in the nasal cavity, paranasal sinuses, or nasopharynx.[207] The recognizable types are typical carcinoid (well differentiated), atypical carcinoid (moderately differentiated), and SmCC neuroendocrine type (poorly differentiated).[208] There are also rare cases that do not fit these categories, and the diagnostic label "neuroendocrine carcinoma, not otherwise specified" may be applied. The limited number of cases published hampers evaluating the ideal treatment strategy.[209–211] A recent study from MDACC reviewed their experience of patients with NEC to determine prognostic factors, treatment strategies, and OS from this rare malignancy.[212] The median age at presentation was 56 years, with equal sex distribution. The majority of patients presented with T3 or T4 disease (78%) and was node

negative (82%). The most common sites of tumor origin were the ethmoid sinus (64%), the nasal cavity (32%), and the maxillary sinus (14%). Approximately half of the cohort received surgery as the primary treatment modality and one-third received chemoradiation therapy. The 5-year OS, DSS, and DFS were 67%, 79%, and 44%, respectively. The incidence of local, regional, and distant failure was 21%, 25%, and 18%, respectively. These results are better than generally reported.[209–211] Predictors of poor outcomes were patients with foveal or orbital involvement and tumor originating outside of the nasal cavity. A complete response to neoadjuvant chemotherapy correlated with improved survival at 3 years.[212] Given the high incidence of distant failure and the chemosensitivity of NEC, neoadjuvant chemotherapy followed by either chemoradiation or surgery and postoperative radiation therapy is a promising strategy. In an earlier report from our institution where eight of 18 patients were treated with neoadjuvant chemotherapy, the OS and local, regional, and distant recurrence were 64.2% and 27.4%, 12.9%, and 12.3%, respectively.[23]

Melanoma.

Malignant melanomas develop from melanocytes derived from the neural crest cells. Although cutaneous melanoma is by far the most common type, melanomas can arise in any organ in which melanin-containing cells are present. Overall, mucosal melanomas remain a rare entity that account for only 0.8% to 3.7% of all melanomas; however, more than half of these cases will arise in the head and neck region most commonly from the sinonasal respiratory mucosa or the oral squamous mucosa.[213] Sinonasal mucosal melanomas (SNMM) are infrequent and account for <1% of all melanomas and up to 4% of all sinonasal malignancies.[214] Epistaxis is the most common presenting symptom followed by nasal obstruction. The lateral nasal wall is the most often affected site, followed by the nasal septum, maxillary sinus, and ethmoid sinus.[213,215–218] Melanomas arising from the nasal cavity had a more favorable prognosis than those arising from other subsites probably related to earlier symptomatology and lower stage of disease at presentation compared to those arising from paranasal sinuses. Unlike cutaneous melanoma, SNMM can be nonpigmented in 35% to 40% of patients.[217,218]

The staging system for sinonasal melanoma has been in evolution. In 1970, Ballantyne introduced a clinical staging system for mucosal

melanomas of the head and neck.[219] This is a simple system that comprises three stages: stage I for local disease, stage II for regional disease, and stage III for distant disease. Although it was widely used, it could not be validated as an independent prognostic factor, mostly because the low percentage of patients who presented with stage II or III. According to Ballantyne's clinical staging system, 76% to 95% of patients with SNMM present with stage I disease.[220] Although the Ballantyne staging system is simple, unfortunately it could not provide prognostic classification because the majority of patients fall in a single category. To address this problem, others have proposed a microstaging system for patients with node-negative disease (Ballantyne stage I) based on histopathologic features such as depth of invasion and tumor architecture.[221,222] These systems have not yet been widely used or validated by others. More recently, Moreno et al.[214] compared the prognostic value of the Ballantyne system with the current AJCC sinonasal staging system in 58 patients with SNMM treated at MDACC. Compared to the Ballantyne system, the AJCC staging system provided an even distribution of the tumor stages (**Fig. 10.58**) and accurately reflected stage-specific prognostic information (**Fig. 10.59A**). The AJCC system has the advantage of being well known by oncologic surgeons and other specialists routinely involved in the care of head and neck cancer patients. Other authors have also described the prognostic value of this staging system in smaller series.[223] On the basis of these findings, we believe that the current AJCC sinonasal staging system should be the primary staging system for patients with SNMM.

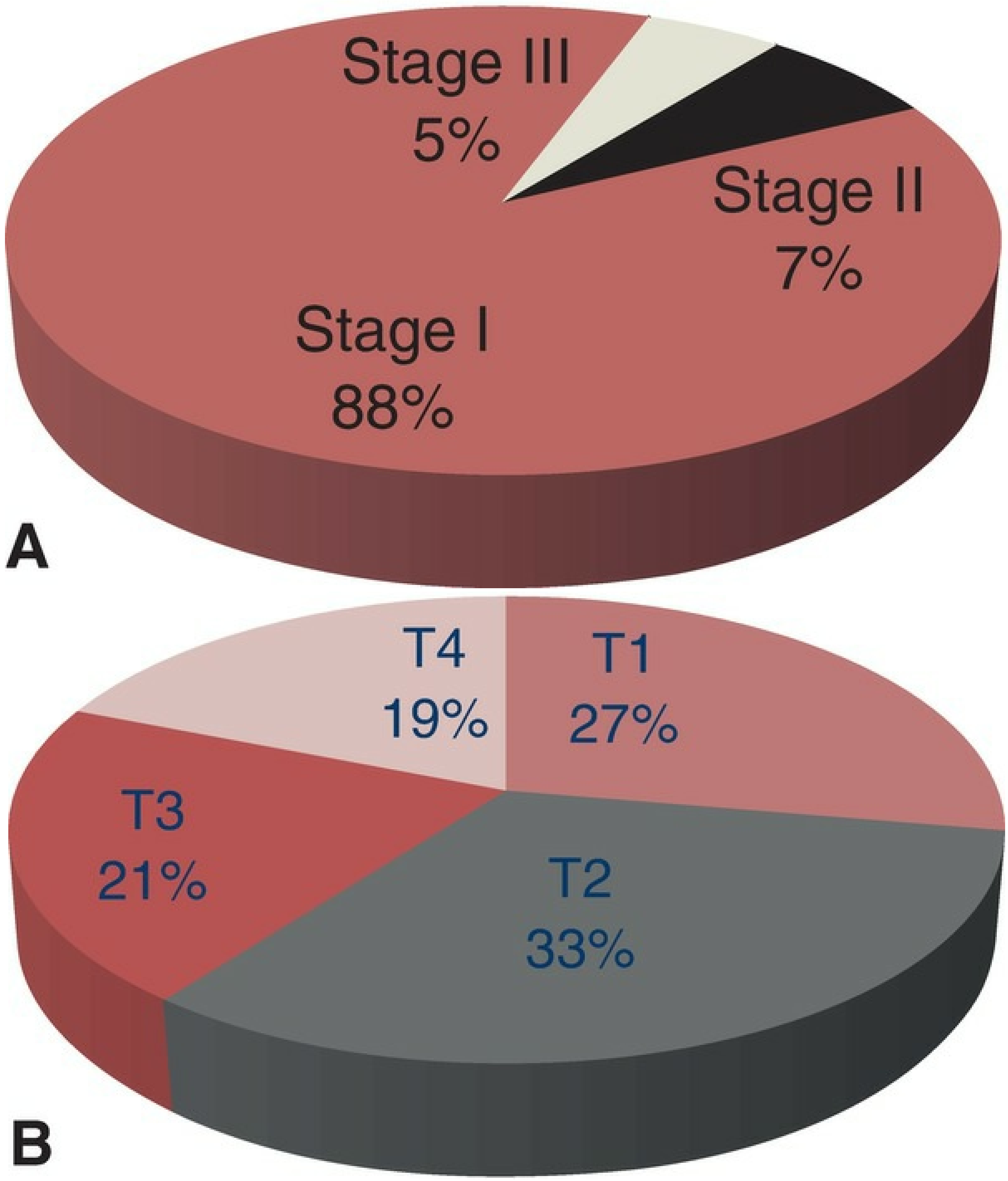
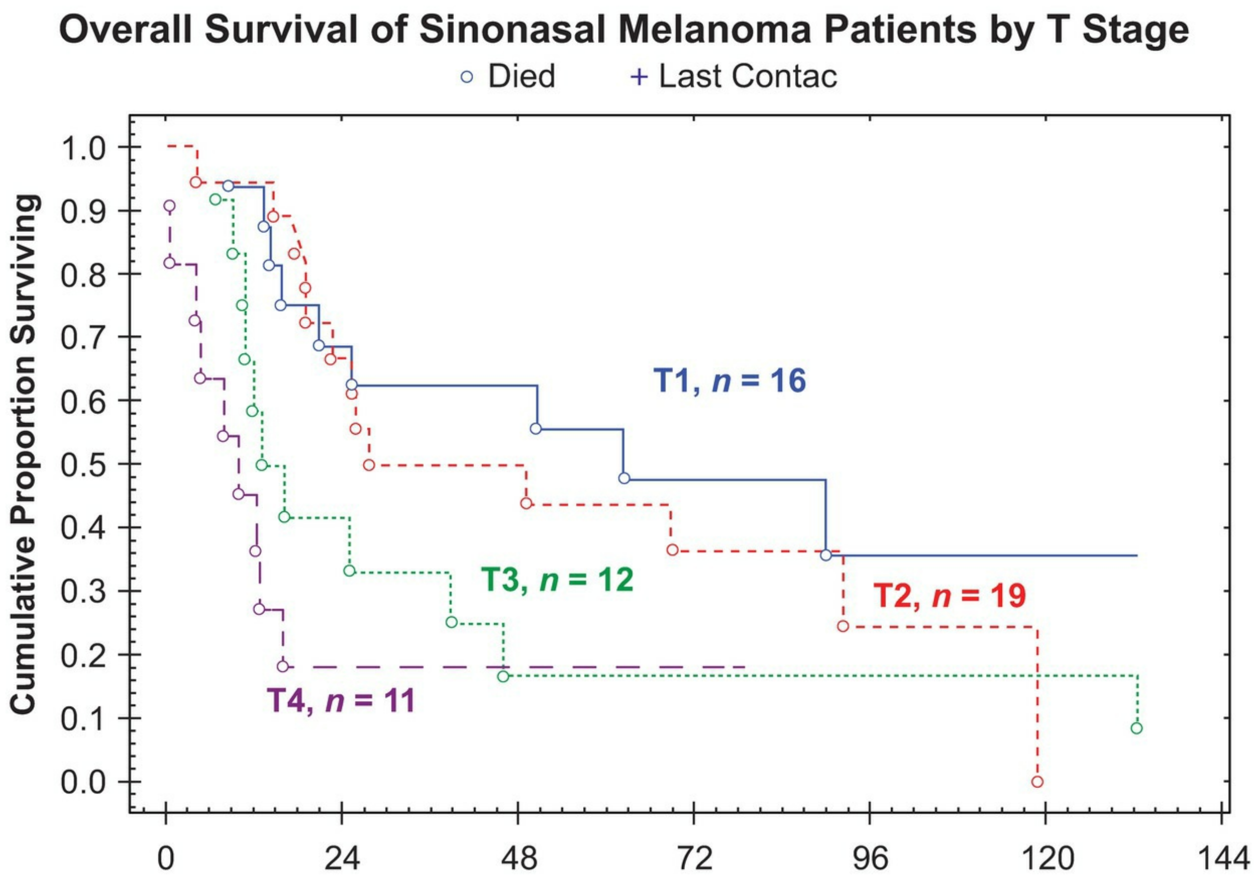
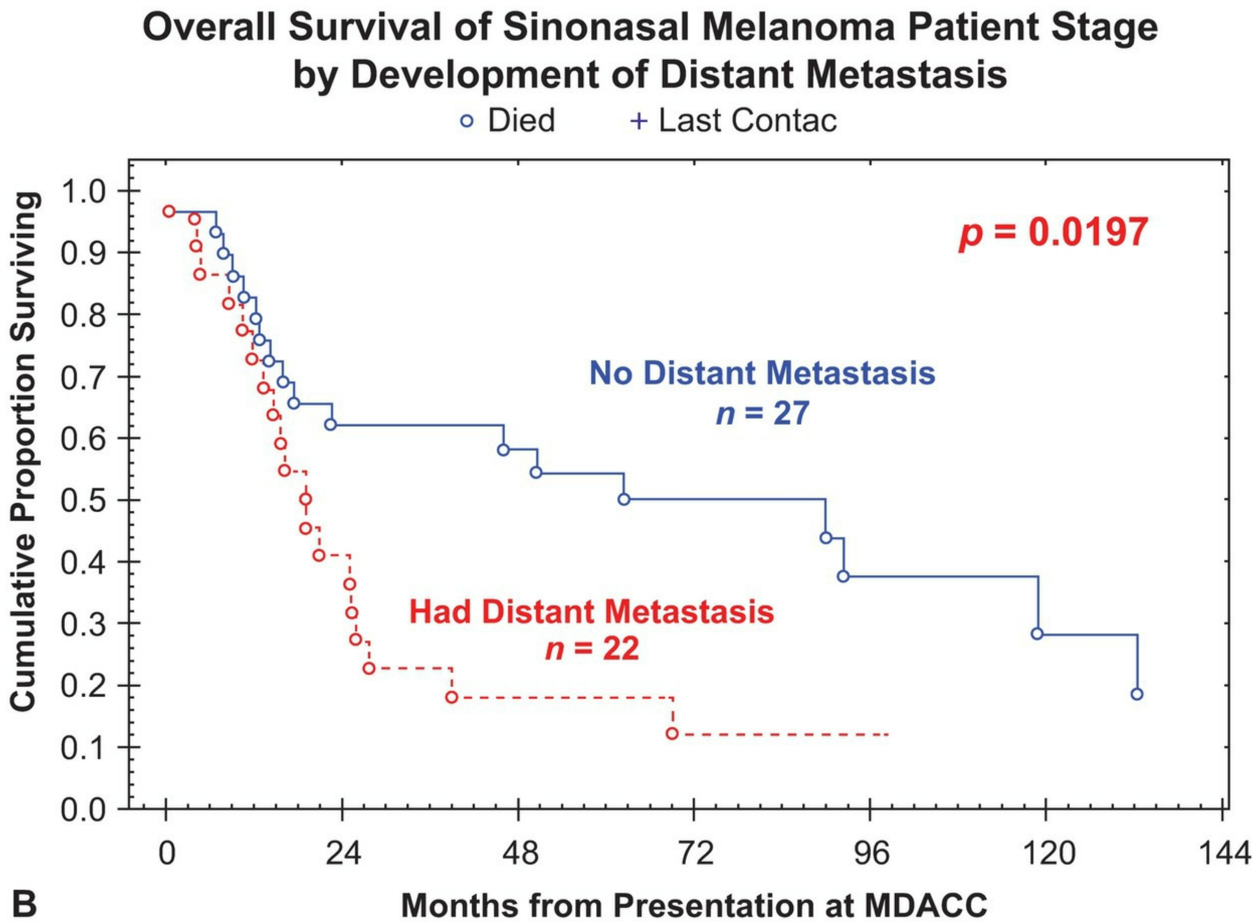


Figure 10.58. Patient distribution according to Ballantyne clinical staging system **(A)** and American Joint Committee on Cancer (AJCC) **(B)** staging system for sinonasal tumors. (Moreno MA, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M.D. Anderson Cancer Center. Cancer. 2010;116(9):2215–2223, Ref. 214.)



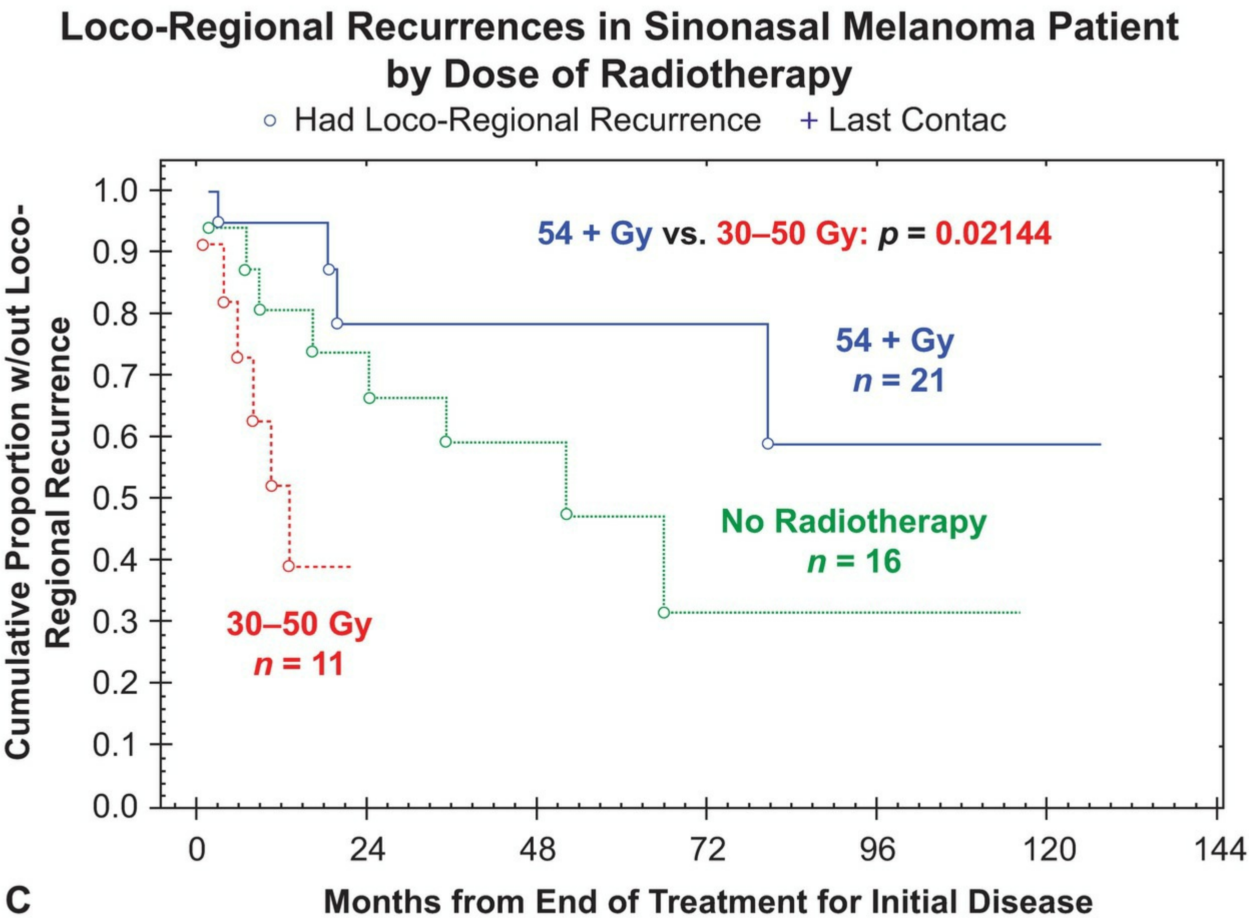
Overall Survival of Sinonasal Melanoma Patients by T Stage
○ Died
+ Last Contac
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
T1, *n* = 16
T2, *n* = 19
T3, *n* = 12
T4, *n* = 11
0
24
48
72
96
120
144
Months from Presentation at MDACC

A



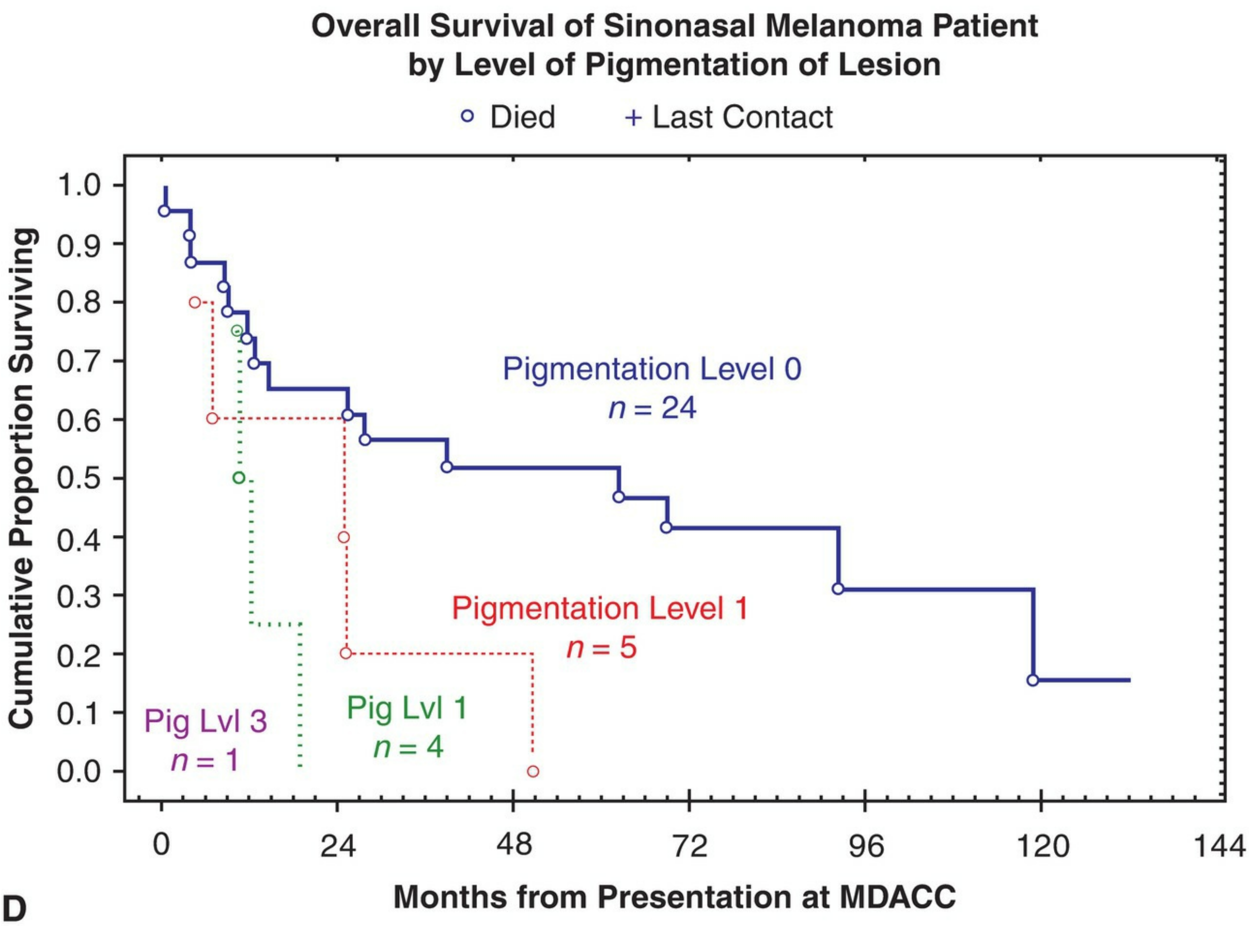
Overall Survival of Sinonasal Melanoma Patient Stage
by Development of Distant Metastasis
Died
+ Last Contac
p = 0.0197
No Distant Metastasis
n = 27
Had Distant Metastasis
n = 22
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
Months from Presentation at MDACC

B



Loco-Regional Recurrences in Sinonasal Melanoma Patient
by Dose of Radiotherapy
○ Had Loco-Regional Recurrence
+ Last Contac
54 + Gy vs. 30–50 Gy: p = 0.02144
54 + Gy
n = 21
No Radiotherapy
n = 16
30–50 Gy
n = 11
Cumulative Proportion w/out Loco-Regional Recurrence
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
Months from End of Treatment for Initial Disease

C


Overall Survival of Sinonasal Melanoma Patient
by Level of Pigmentation of Lesion
Died
+ Last Contact
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Pigmentation Level 0
n = 24
Pigmentation Level 1
n = 5
Pig Lvl 3
n = 1
Pig Lvl 1
n = 4
0
24
48
72
96
120
144
Months from Presentation at MDACC

D

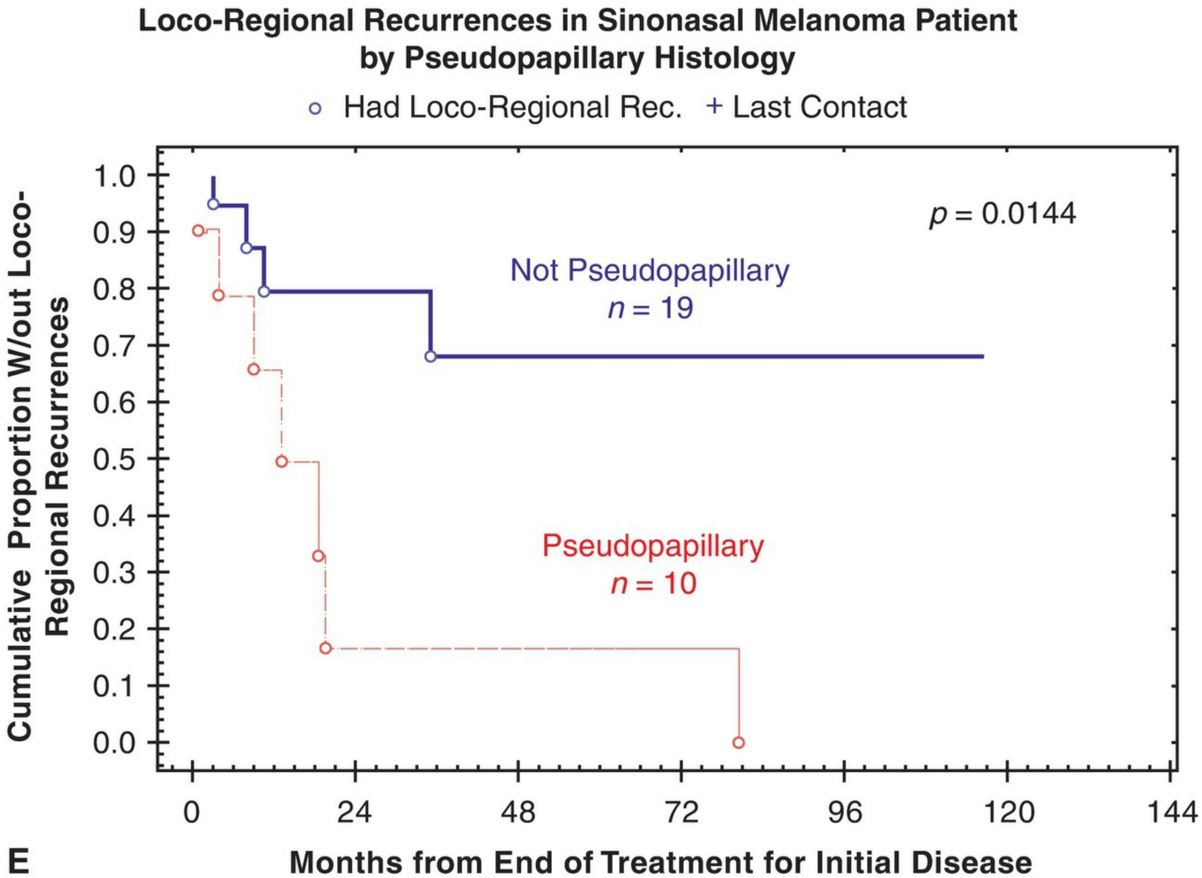


Figure 10.59. Outcomes of patients with sinonasal melanoma treated at MDACC. **A:** Survival by AJCC stage. **B:** Effect of distant metastasis on survival. **C:** Effect of radiation dose on disease recurrence. (Moreno MA, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M.D. Anderson Cancer Center. Cancer. 2010;116(9):2215–2223, Ref. 214.) **D:** Effect on level of pigmentation on survival. **E:** Effect of histologic pattern on survival.

Complete tumor excision is widely accepted as the standard of care for treatment of patients with SNMM. The invasive and locally advanced nature of these tumors coupled with the anatomical complexity of the sinonasal passages and proximity to vital structures makes a complete resection difficult in most cases. Surgical margins are described as microscopically positive or close (within 1 mm) in more than 20% of patients. Although negative margins are associated with better local disease control, the impact of surgical margins on survival is less clear. The potential benefits of negative margins of improved local control may be concealed by the development of distant metastasis in a significant number of patients with a

profound negative impact on survival (**Fig. 10.59B**).[214] In this context, the optimal surgical approach will depend on the location and extent of tumor. The surgeon's experience and thorough knowledge of the anatomy are key to achieve a successful oncologic resection with a minimum cosmetic and functional impact. Elective treatment of the neck is usually not performed, as the incidence of nodal disease at the time of presentation is relatively low, ranging from 6% to 25%.[213] The use of sentinel lymph node mapping and biopsy has proven beneficial in cutaneous melanoma but has only been minimally explored in mucosal melanomas.[224]

The available evidence suggests that the use of adjuvant radiation therapy improves locoregional control, although there is no evidence of benefit in OS.[220,223,225,226] To date, there is no consensus regarding the indications for postoperative radiation therapy, although most authors agree regarding its use in patients with positive and close margins, especially as these have been recently identified as negative prognostic factors. Radiobiologic studies show a high heterogeneity in behavior of irradiated melanoma cells, and to date, the optimal total dose and fractionation schemes for SNMM are also not well defined.[226] In cutaneous melanoma, there is evidence suggesting that hypofractionation schemes may improve tumor response rate and decrease treatment toxicity, but prospective randomized trials have failed to support these findings. In a recent study from MDACC, the use of postoperative radiation improved locoregional control but only when a total dose >54 Gy was used (**Fig. 10.59C**).[214] A similar improvement was observed when a standard fractionation schedule was used versus hypofractionation. It is difficult to determine whether the lack of improvement for the group that received a lower dose was determined by total RT dose, hypofractionation, or a combination of both. In contrast with these findings, other authors have reported that hypofractionation might improve local control and OS in head and neck mucosal melanomas.[227] In the future, a better understanding of the radiosensitivity of this rare tumor and the availability of new technical radiation modalities might allow for better incorporation of radiotherapy into a multimodality treatment strategy.

There is no standard systemic therapy recognized as optimal for the treatment of patients with SNMM, and studies of systemic therapy focused on SNMM are scarce. Bartell et al.[228] reported the experience of 15 patients treated with biochemotherapy for advanced head and neck mucosal

melanoma at the MDACC. In this study, 11 patients presented with distant metastasis and 4 had locoregional recurrence or bulky, unresectable disease. The overall response rate for the series was 47% with a complete response rate of 27% and a median OS of 22 months. Biochemotherapy was associated with severe but manageable toxicity including severe pancytopenia in all patients, but there were no treatment-related deaths. The authors concluded that biochemotherapy should be considered not only for metastatic disease but also as neoadjuvant therapy in patients with extensive locoregional disease.

The 5-year OS of patients with SNMM is poor and ranges from 20% to 35% among different reports and has not changed significantly over the last several decades.[213] Given the rarity of this tumor, most series extend retrospectively several decades to gather an adequate number of patients. For example, a recent review of the U.S. National Cancer Institute's SEER registry identified 567 patients with SNM between 1973 and 2009.[229] DSS at 5 years was 37% for patients diagnosed with nasal cavity disease, 24% for patients with maxillary sinus tumors, and 18% for patients with ethmoid sinus disease. Patients showing evidence of overlapping sinus involvement had approximate 1-year survival of 54%, and none survived beyond 49 months. Unfortunately, such survival analysis of patients who were treated over a time period that spans almost five decades may fail to reflect the advances in diagnosis and treatment that might have occurred in recent years. For this reason, investigators from MDACC sought a review of SNMM limited only to the most recent 15 years to capture contemporary data that more accurately reflect the current status of this disease.[214] For the 58 patients with SNMM, 2-year OS was 69% for T1, 67% for T2, 33% for T3, and 18% for T4 (Fig. 10.59A); these differences were statistically significant ($p = 0.0183$). Differences in 5-year survival between these groups did not reach statistical significance ($p = 0.2067$), except when combining T1/T2 versus T3/T4 ($p = 0.0096$). Patients with negative margins had a better 2-year survival (64% vs. 42%) and 5-year survival (44% vs. 25%), although this difference did not reach statistical significance ($p = 0.1534$ and $p = 0.2169$, respectively). Local recurrence developed in 42% of the patients with positive margins versus 20% of those with negative margins ($p = 0.2657$). The study also suggested that certain histopathologic features correlated with outcome. The presence of melanin pigment was a highly significant outcome

predictor (0% vs. 48% 5-year survival; $p = 0.0183$). Even more, the level of pigmentation of the lesion was correlated with a worse clinical outcome, as shown in Figure 10.59D. The presence of 10 or more mitosis per HPF appeared to be an outcome predictor. All except 1 of the 20 patients who had >10 mitoses per HPF died of disease or presented with locoregional recurrence. In contrast, all the patients who had a complete response to biochemotherapy were among those with 10 mitoses per HPF or less. As is shown on Figure 10.59E, the presence of a pseudopapillary architecture was associated with a higher rate of locoregional failure ($p = 0.0144$) but did not affect survival ($p = 0.4909$).

In recent years, several molecular markers have emerged as potential prognostic indicators. The Ki67 antigen is an indicator of proliferative activity that has been associated with prognosis in cutaneous melanoma among other tumors. Recently, Kim et al.[230] reported that patients with more than 35% for Ki67 staining had a survival advantage over those with scores of more than 35% in a series of 27 sinonasal melanomas. The abnormal expression of caspases and inhibitor of apoptosis proteins is thought to be the cause of apoptotic dysfunction in melanoma. The nuclear expression of survivin, an inhibitor of apoptosis protein, has been associated with higher recurrence rates and poor survival in cutaneous melanoma. In a recent review of 77 patients with melanoma, 25 of them of mucosal origin, Chen et al.[231] reported the prognostic value of nuclear expression of survivin-C and survivin-N. They found that this is an indicator independent of tumor stage and location (mucosal vs. cutaneous) and appears to be superior to Ki67 immunostaining in multivariate models. Genetic mutations involving the receptor tyrosine kinase KIT have been associated with some types of melanoma. Specifically, c kit, a protein encoded by the KIT proto-oncogene melanoma, is thought to play a role in early stages of oral mucosal melanoma tumorigenesis. There is emerging evidence indicating that melanomas with KIT activation may also respond to KIT inhibitors already in use such as imatinib or dasatinib.[228] The role of these therapeutic agents in SNMM needs to be investigated further, but, if confirmed, it would represent a paradigm-shifting entry into the era of personalized medicine in which therapy can be tailored to mechanistically relevant changes in cancer cells of this deadly disease.

Sarcomas.

Sarcomas account for 10% to 15% of SNT malignancies and comprise a wide array of tumors of mesenchymal origin.[232] The most common primary sites of origin are the maxillary sinus followed by the ethmoid sinus. Sarcomas of soft tissue origin account for ~80% of cases, whereas bony or cartilaginous sarcomas are less frequent.[233] Five-year OS for sinonasal sarcomas in large-group analyses ranges between 46% and 67%. However, survival is significantly dependent on histology and the histologic grade of tumor.[232,234–236] Rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma are examples of high-grade tumors with 5-year OS reported between 33% and 70%. Low-grade tumors such as hemangiopericytoma, chondrosarcoma, and leiomyosarcoma have a more favorable reported 5-year OS of 64% to 94%.[232,233,235,237,238] High-grade lesions account for the majority of sinonasal sarcomas in both the pediatric and adult populations with rhabdomyosarcoma and osteosarcoma comprising between 47% and 73% of sinonasal sarcomas.[232–234,239]

In a recent study of the SEER database, 352 patients with sinonasal sarcomas, diagnosed from 1973 to 2008, were analyzed.[232] The influence of patient age, gender, race, and prior irradiation, as well as tumor histology and subsite, on outcome was reported. The mean age was 44 ± 28 years, and the patients were fairly evenly distributed among the age groupings. The majority (78%) of patients were identified as white, 12.5% were identified as black, and 10% were classified as other. The majority of tumors were located within the maxillary sinus (58%), followed in frequency by the ethmoid (22%) and sphenoid sinus (13%). Rhabdomyosarcoma was the single most common tumor histology (34%), followed by miscellaneous soft tissue malignancy (31%) and miscellaneous fibromatous malignancy (16%). Approximately half of the patients received radiation postoperatively. Median follow-up was 28 months (25th percentile = 12 months, 75th percentile = 83 months). Of the 352 total patients, 192 (55%) died over the follow-up period. The 1-, 5-, and 10-year survival probabilities were 78.8%, 47.4%, and 38.1%, respectively. Median survival time was 50 months. Males had a significantly lower median length of survival and 5-year survival (42.5% vs. 53.1%) than female sarcoma patients (35 vs. 74 months). Females had a roughly 32% decrease in the rate of mortality compared to males (HR = 0.68, $p = 0.0153$), controlling for the other factors. Neither race nor radiation therapy were significantly associated with mortality. Survival declined with increasing age. The 5-year

survival for patients younger than 10 years was 63.1%, whereas the 5-year survival for patients older than 80 years was 26.8%. In general, older age was associated with a significant decrease in the median survival time and 5-year survival rate. The HR became successively larger with each older age category. For example, patients aged 10 to 49 years had a 1.84 times greater rate of mortality compared to patients aged <10 years after controlling for the other factors, whereas patients aged 50 to 69 years had a 2.78 times greater rate, and patients >80 years had the highest HR with 10.8 times higher mortality rate. For histology, chondrosarcoma was associated with lowest mortality rates after controlling for the other factors and was therefore chosen as the reference group for the purpose of the analysis. Five-year survival for chondrosarcoma was 64.4%. Kaposi sarcoma patients had a 5.53 times greater rate of mortality (HR = 5.53, $p = 0.0051$, 5-year survival 20.0%), whereas rhabdomyosarcoma patients had a 3.62 times greater rate of mortality (HR = 3.62, $p = 0.0018$, 5-year survival 32.9%) compared to chondrosarcoma patients. Clearly, the natural history, treatment strategies, and prognosis are dependent primarily on the histopathologic type of sarcoma, and the reader is referred to the details of management and outcome discussed in the chapter dedicated to sarcomas of the head and neck.

Lymphoma.

Primary non-Hodgkin lymphoma (NHL) of the SNT accounts for <10% of all NHLs and comprises three main pathologies: diffuse large B-cell lymphoma (DLBCL), natural killer/T-cell lymphoma (NKTCL), and T-cell lymphoma (TCL).[240,241] Although DLBCL is the most common form of sinonasal NHLs in the Western population, NKTCL is the predominant variant in Asia, with both also demonstrating different epidemiologic patterns and symptomatology.[242] DLBCL most commonly affects patients over 60 years of age and has a predilection for paranasal sinus origination with between 37% and 75% arising from the maxillary sinus.[241–243] NKTCL, on the other hand, occurs in a younger subset of patients, median age of 45 years, with ~67% to 80% originating in the nasal cavity and <30% involving the paranasal sinuses.[240,243,244] The high rate of nasal cavity involvement in NKTCL, also known as lethal midline granuloma, is associated with the classic presentation of the disease characterized by destruction of the nose and midline facial structures. Other differences in presentation and diagnosis include the relative absence of B symptoms in DLBCL while present in up to

29% of cases of NKTCL, as well as the significant association of EBV with NKTCL (up to 92%).[240,243,244]

Treatment of NHL of the paranasal sinuses is chemotherapy and radiation therapy. The chemotherapeutic agents utilized between DLBCL and NKTCL differ, however, NKTCL expresses high levels of P-glycoprotein conferring multidrug resistance.[245] As such, CHOP-based chemotherapeutic regimens (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone) are generally utilized in DLBCL, whereas regimens containing agents unaffected by P-glycoprotein (L-asparaginase, vincristine, prednisone) are recommended for NKTCL.[240,242,245] Early-stage disease is most often treated with concurrent chemoradiation therapy or chemotherapy with sandwiched radiotherapy. Late-stage and disseminated disease may only be amenable to systemic therapy. Hematopoietic stem cell transplant is reserved for late-stage, nonnasal, disseminated, or relapsed lymphomas where remission has been achieved.[245] Five-year OS of sinonasal DLBCL ranges between 50% and 68%, whereas sinonasal NKTCL demonstrates 5-year OS of <40%.[240–244] Patients able to achieve a complete response after primary therapy show significantly improved OS compared to those who do not, even accounting for locoregional or distant disease on presentation.[240] In a recent study, the SEER database was searched for patients diagnosed with sinonasal NKTCL and DLBCL between 1973 and 2011. Data analyzed included patient demographics, incidence, treatment modality, and survival.[246] Three hundred and twenty-eight sinonasal NKTCL cases and 1,054 sinonasal DLBCL cases were identified. The mean ages at diagnosis for NKTCL and DLBCL were 51.7 and 67.8 years, respectively ($p = 0.0001$). Overall 1-, 5-, and 10-year DSS rates for DLBCL were 85.5%, 63.5%, and 44.0%, compared to 66.4%, 30.9%, and 9.2% for NKTCL, respectively ($p < 0.0001$). For patients matched for stage, age, and treatment modality, the 1-, 5-, and 10-year DSS for the DLBCL group were 94.4%, 72.8%, and 46.8%, respectively, whereas the respective survival rates for the NKTCL group were 77.6%, 38.4%, and 13.9%, respectively ($p < 0.0001$ at each time interval). This large population-based comparison between sinonasal DLBCL and NKTCL demonstrated that DLBCL has a better prognosis regardless of gender, stage, treatment modality, and age. For detailed discussion of the management and outcomes, the reader is referred to the chapter on Lymphomas of the Head and Neck.

Metastasis to the Sinonasal Tract.

Involvement of the SNT with metastatic deposits is a rare phenomenon with <200 reported cases in the literature. Hematogenous spread to the paranasal sinuses is the most common form of delivery. Renal cell carcinoma is the most common malignancy to metastasize to the SNT, followed by breast, lung, and prostate cancer. Tumors that rarely metastasize to the SNT including follicular thyroid carcinoma, hepatocellular carcinoma, and colorectal carcinoma have also been reported.[247] Metastasis to the sinonasal region may be the first clinical evidence of the primary tumor, or it might appear after treatment of the primary neoplasm. Although the maxillary antrum is the most frequent site for metastasis, any area of the SNT may be involved. Treatment is palliative and is indicated for the relief of pain, bleeding, or orbital complications.[248]

OUTCOME AND PROGNOSIS

Although the literature is replete with reports describing the outcome and prognosis of patients with sinonasal cancer, several confounding factors make meaningful interpretation of the results extremely difficult. Such factors include the diversity of histologic diagnoses, site of origin, extent of tumor invasion, prior therapy, extent of surgical resection, status of surgical margins, adjuvant therapy, and length of follow-up. The greatest factor influencing prognosis is the histopathologic type of sinonasal malignancy. This has a direct bearing on the biology and natural history of the disease and consequently the outcome of therapy. This is highlighted in **Figure 10.60** showing the 5-year survival by histology for 2,698 patients with sinonasal cancer seen at MDACC from 1944 to 2007. For example, ENB and adenocarcinoma have significantly better survival than melanoma and SNUC. As discussed in the section on tumor-specific consideration, even among patients with same tumor type, histopathologic grade has a significant impact on survival, for example, Hyams grade for ENB (Fig. 10.53), tumor pattern in ACC (tubular, cribriform, and solid) (Fig. 10.52D), tumor characteristics in melanoma such as pigmentation and psuedopapillary features (Fig. 10.59D and E), and tumor differentiation in NEC. These are examples of the need for accurate grading of sinonasal tumors within the same histopathologic type.

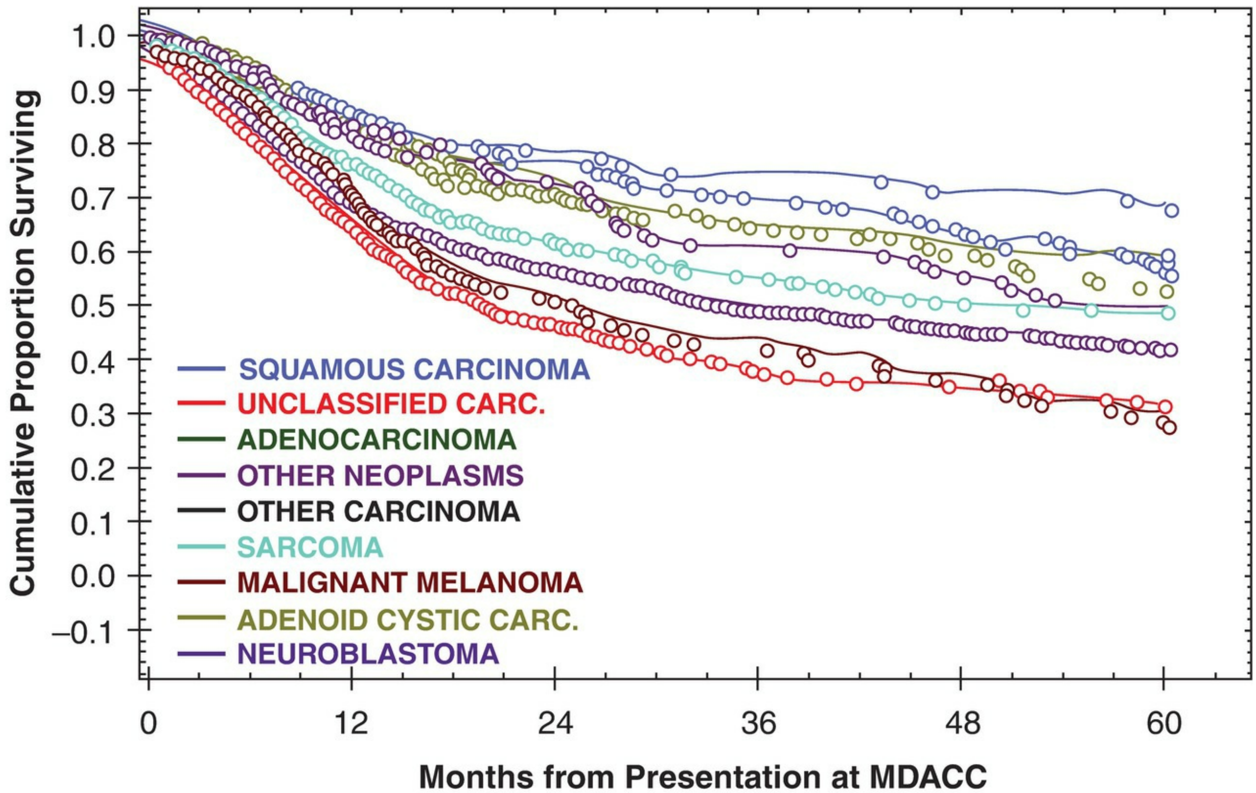
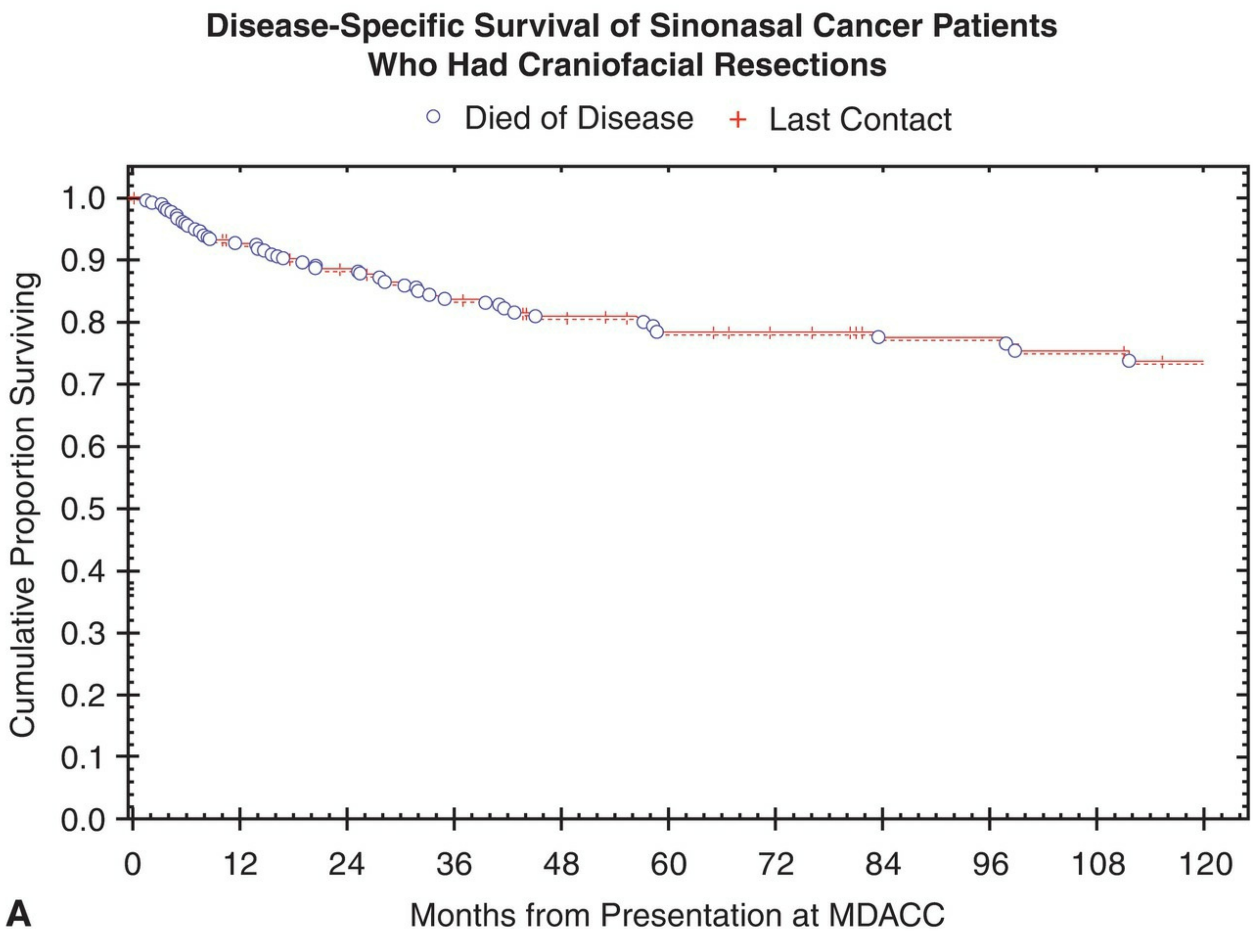
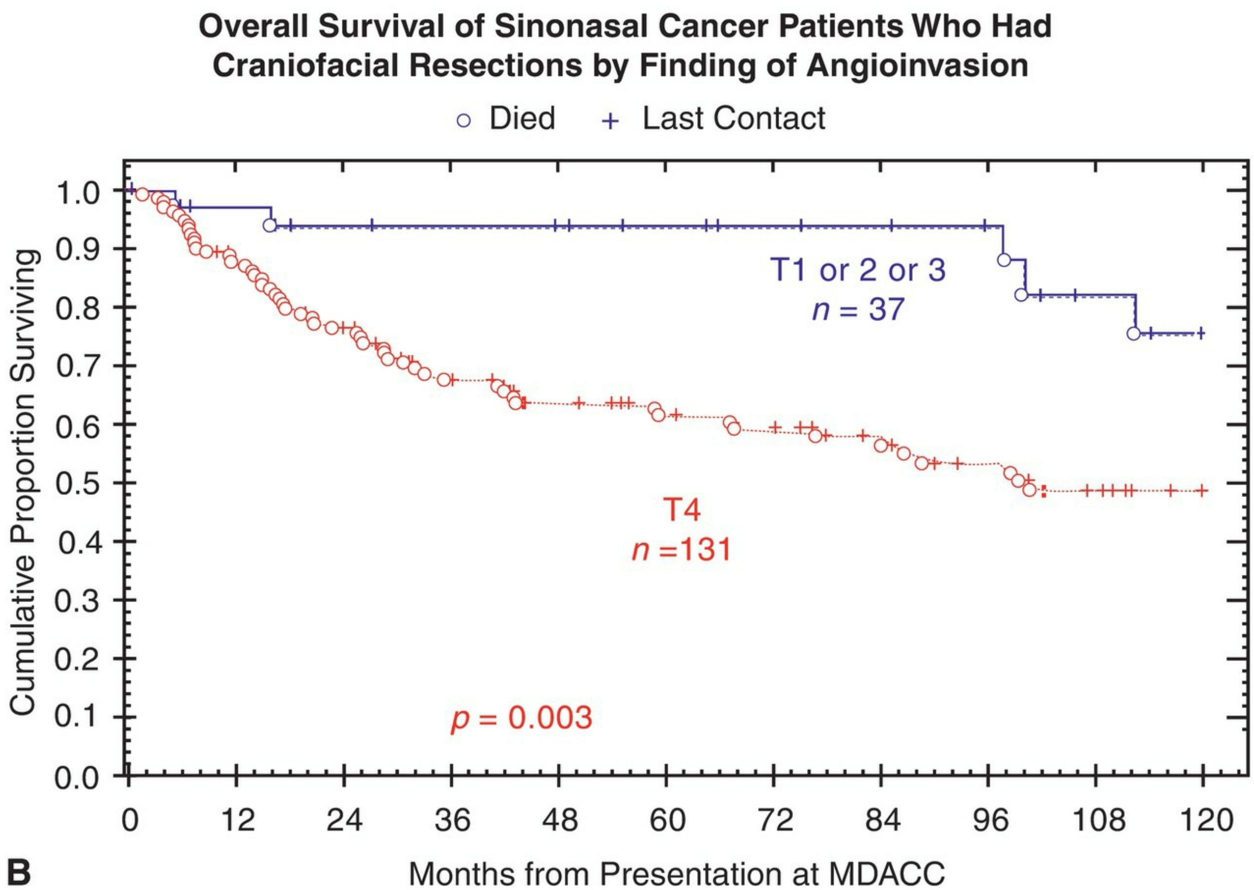


Figure 10.60. Overall 5-year survival by histology of 2,698 patients with sinonasal cancer seen at MDACC from 1944 to 2007.

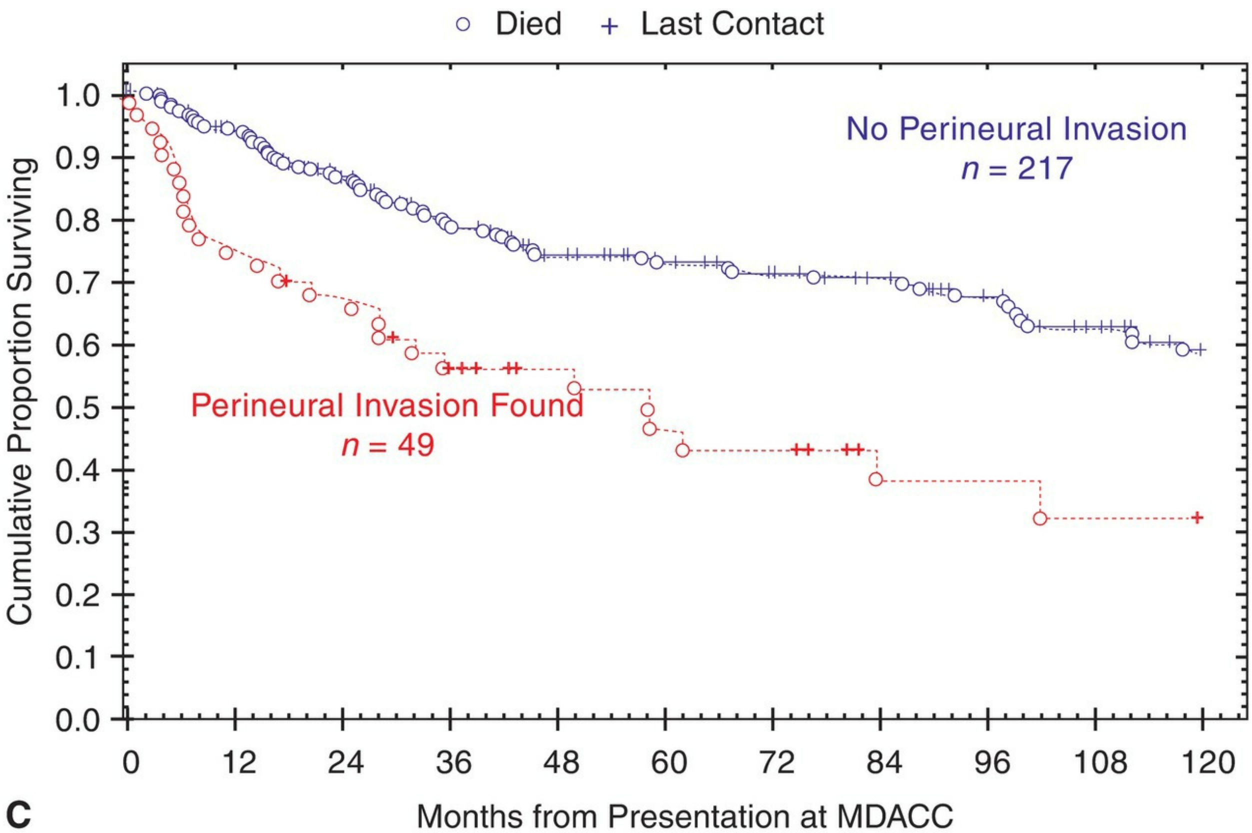
The multidisciplinary integration of modern techniques of skull base surgery, microvascular reconstruction, conformal radiation, and chemotherapy improved the overall outcome of patients with sinonasal malignancy (Fig. 10.1). The 10-year survival outcomes of patients undergoing anterior craniofacial resection for sinonasal cancer at MDACC in the last decade are shown in **Figure 10.61A**. Despite these excellent outcomes, patients with T4 tumors have a worse prognosis (**Fig. 10.61B**). The presence of PNI (**Fig. 10.61C**) and angioinvasion (**Fig. 10.61D**) also has negative impact on survival. Brain invasion has a particularly profound, and perhaps the most dramatic, impact on survival (**Fig. 10.62A**). This probably has to do with the difficulty achieving negative surgical margins, which is a major determinant of a favorable outcome in surgically treated patients (**Fig. 10.62B and C**). It is interesting to note that the effect of method of resection (en bloc vs. piece meal) did not affect the outcome as long as the margins were negative (**Fig. 10.62D**). Several molecular and genetic markers of prognosis have been already discussed in corresponding tumor-specific section. The presence of cervical lymph node metastasis from sinonasal

cancer is an uncommon event, but when it is present, survival is reduced by at least 50%. Finally, the presence of distant metastasis is usually an indication that the disease is incurable and treatment strategies should focus on palliation.




Overall Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections by Finding of Angioinvasion
○ Died + Last Contact
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
T1 or 2 or 3
n = 37
T4
n =131
p = 0.003
0 12 24 36 48 60 72 84 96 108 120
Months from Presentation at MDACC
B

Overall Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections by Finding of Angioinvasion



C

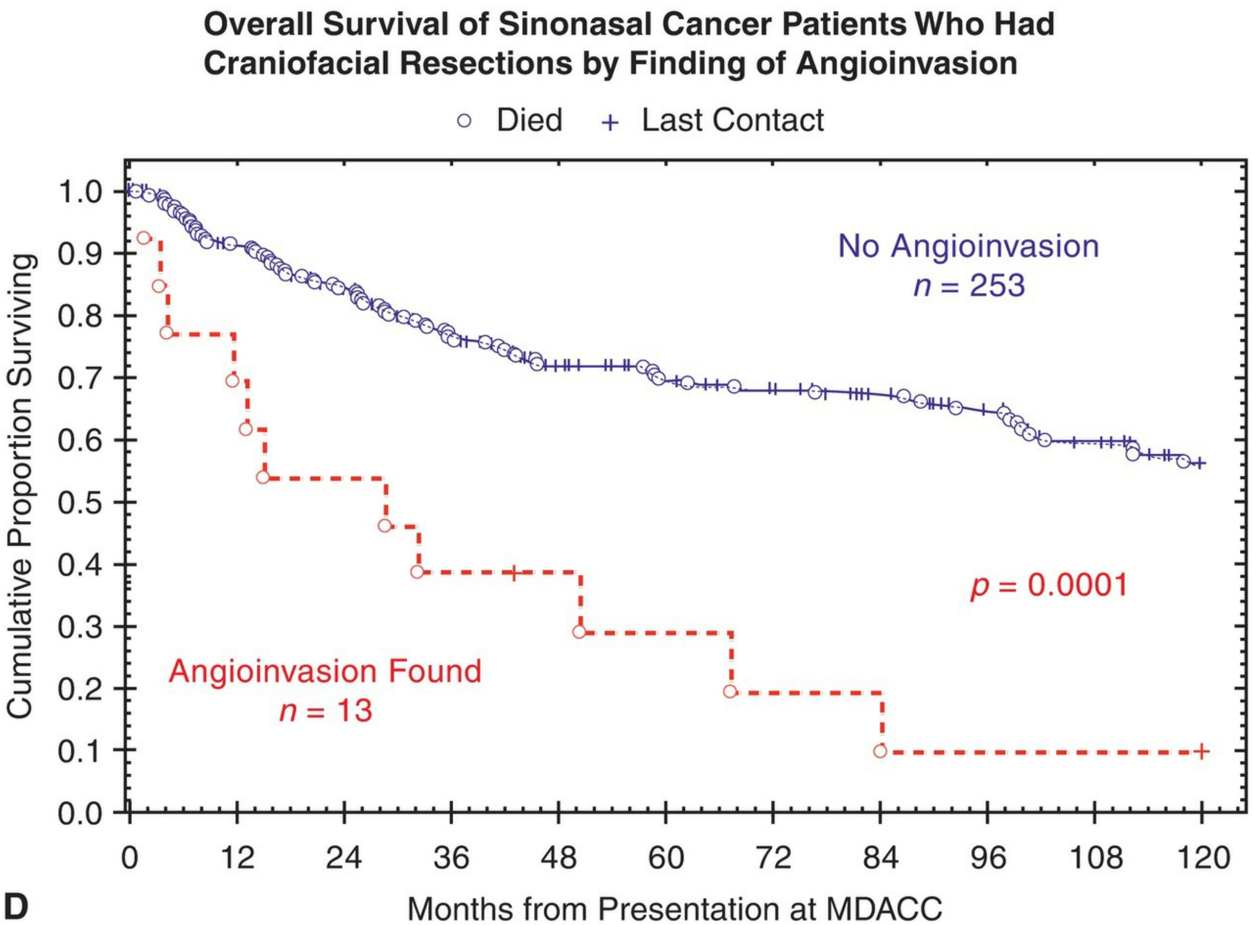


Figure 10.61. Survival outcomes of craniofacial resection in patients treated at MDACC in the last decade. **A:** Ten-year disease-specific survival. **B:** Effect of stage on survival. **C:** Effect of PNI on survival. **D:** Effect of angioinvasion on survival.

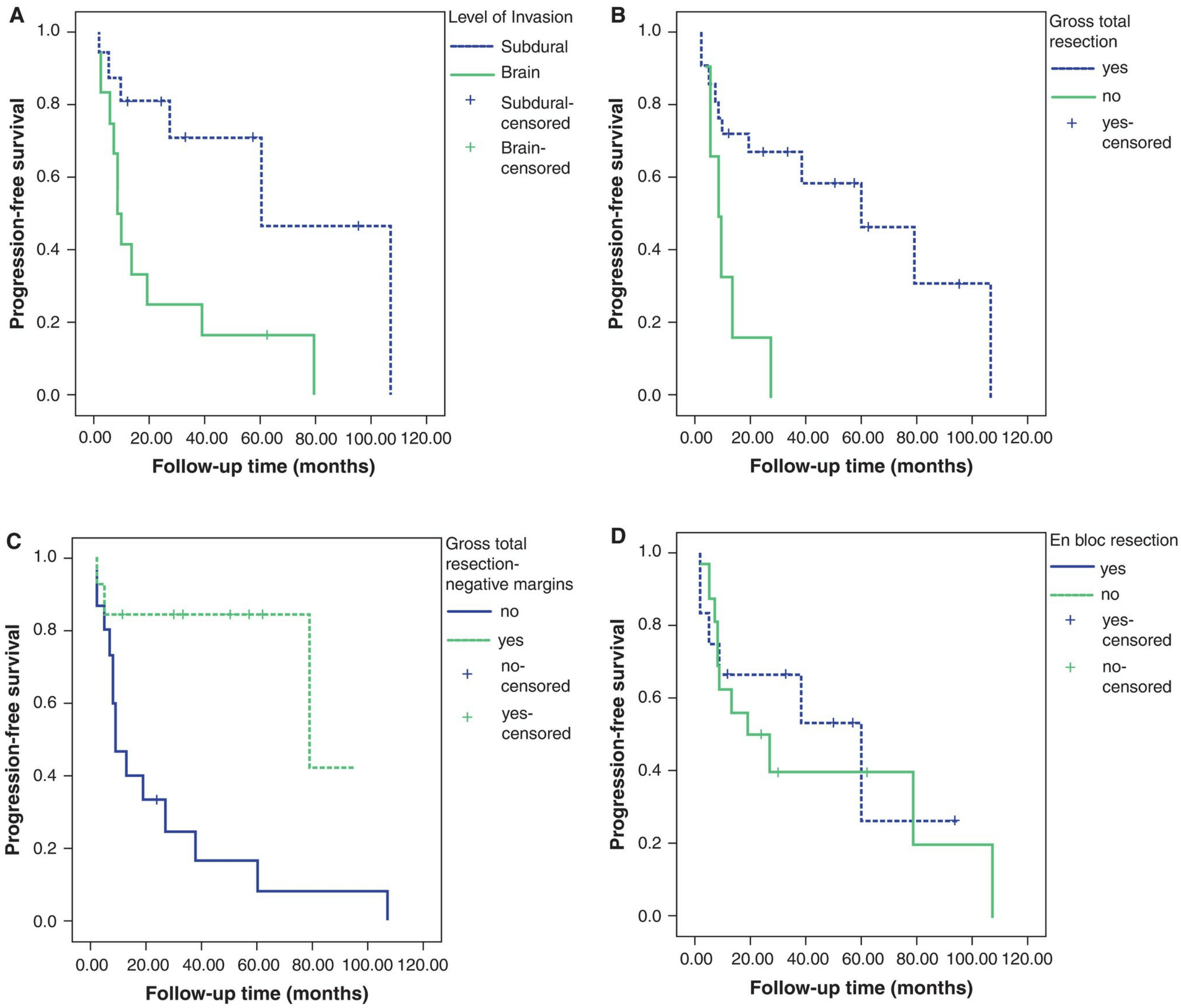


Figure 10.62. Prognostic significance of transdural invasion of cranial base malignancies in patients undergoing craniofacial resection. **A:** Brain invasion was a significant prognostic factor associated with PFS (p = 0.005). **B:** A significant association was found for PFS and gross total resection (GTR) (p = 0.003). **C:** In the cohort of patients with GTR, the ones with a microscopic negative surgical margin had a better PFS than those with positive margins (p = 0.02). **D:** No significant association was found for PFS between en bloc and piecemeal resection (p = 0.64). (Feiz-Erfan I, et al. Prognostic significance of transdural invasion of cranial base malignancies in patients undergoing craniofacial resection. Neurosurgery. 2007;61(6):1178–1185; discussion 1185, Ref. 53.)

SUMMARY

Progress in prognosis of patients with nasal and paranasal carcinoma has been made during the last 40 years (Fig. 10.1). This is probably due to advances in both the evaluation and treatment of these patients. Office endoscopy and high-resolution imaging allow better assessment of the extent of disease and hence better treatment planning. Advances in cranial base surgery and microvascular reconstruction have allowed more adequate resection of advanced sinonasal cancer, even if it involved the cranial base. Improvements in the delivery of radiation therapy using highly conformal radiation such as IMRT or proton therapy have allowed more targeted and homogenous dosimetry to the tumor while sparing nearby critical structures. The integration of more effective chemotherapeutic and targeted agents in the overall management of patients with sinonasal cancer has improved local control of the disease.

Despite these improvements, cancer of the paranasal sinuses remains a difficult and challenging problem. The vast majority of patients still present with advanced stage disease, as the paucity and nonspecific nature of their signs and symptoms from smaller tumors hamper early diagnosis of the disease. The propensity for early spread to surrounding critical structures, such as the cranial base, orbit, and brain, increases the complexity and morbidity of treatment while reducing its efficacy. These factors continue to impede further improvement of treatment outcome, and a significant number of patients still succumb to the disease. Therefore, the most effective strategy to further improve the treatment outcome of patients with cancer of the nasal cavity and paranasal sinuses is earlier detection of disease.

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11 Nasopharyngeal Carcinoma

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Background

Introduction

Nasopharyngeal carcinoma (NPC) has a unique epidemiology and pathogenesis, and the treatment of NPC has undergone several paradigm shifts over the last 30 years. Advances in the planning and delivery of radiotherapy (RT) and the adjunctive use of chemotherapy over the decades have all contributed to the improved prognosis of NPC. In Hong Kong where NPC is among the top 10 most common cancers with an age-adjusted mortality rate of 3.9 per 100,000 persons, the 5-year overall survival (OS) of patients with stage I and II NPC now approaches 90%.[1] However, worldwide, up to 65,000 people still died of NPC annually in recent times.[2,3] This is mainly due to the fact that 20% of patients with locoregionally advanced (i.e., stage III and nonmetastatic stage IV) NPC will invariably develop distant metastases despite modern treatment. In Hong Kong, the 5-year OS for nonmetastatic stage III and IV is ~60% in patients who were treated with 2-dimensional (2D) RT.[1,4] For patients with metastatic NPC, the median OS (12 to 18 months) is still well short of that of other cancers such as metastatic colorectal cancer (over 20 months) following modern drug therapy. Although concurrent chemoradiotherapy has significantly improved the treatment outcome for patients with stage III and nonmetastatic stage IV NPC, this approach also increases the incidence of certain acute and late toxicities. Thus, newer biomarkers and more accurate staging are needed to identify those patients who are most likely to benefit from multimodal therapy.

On a global scale, NPC is a rare cancer with ~80,000 new cases reported

per year and accounts for 0.7% of all cancers.[2] In nonendemic areas like North America and Europe, the incidence rate is <1 case per 100,000 populations. This is in marked contrast with the endemic or “high-risk” areas such as Hong Kong and Southern China, where the annual age-standardized incidence rates are as high as 20 to 30 cases per 100,000 population in men and 8 to 15 cases per 100,000 population in women.[5,6] Recent studies have suggested a fall in the incidence of NPC in the last 30 years in China. However, other reports have found a stable to rising incidence in certain parts of Southern China.[5,7] According to the Hong Kong Cancer Registry,[3] the age-standardized incidence rates of NPC in 2010 have decreased from 12.8 cases per 100,000 population in 2001 to 8.7 cases per 100,000 population for both sexes. Several studies have speculated on the reasons for this declining trend in Hong Kong. One report found that only the incidence rate of the keratinizing subtype of NPC has fallen, whereas the rate of the more common nonkeratinizing subtype has remained relatively stable.[8] Other studies have attributed the falling incidence to improvements in socioeconomic status and standard of living in the local population, as well as an improvement in the standards of medical care in Hong Kong.[1,9]

NPC is classified into different histologic subtypes: type 1 (I) squamous cell carcinoma, type 2a (II) keratinizing undifferentiated carcinoma, and type 2b (III) nonkeratinizing undifferentiated carcinoma. The World Health Organization (WHO) III subtype is the most common form of NPC in endemic areas and is ubiquitously associated with the Epstein-Barr virus (EBV). It also differs from WHO I NPC with regard to its sensitivity to chemotherapy and RT. The staging of NPC is based on the depth of invasion of the soft tissue, cranial nerves, and bony structures at and near the nasopharynx by the primary tumor, the involvement of local and regional lymph nodes of the head and neck, and the presence of distant metastases. In Hong Kong, the distribution of stage groups at presentation is as follows: stage II 7%, stage IIA to B 41%, stage III 25%, and stage IVA to B 28%. This means that nearly half of all patients with NPC in Hong Kong present at an advanced stage; hence, much of the clinical research in NPC has been focused on improving the treatment of advanced NPC.

Staging of Nasopharyngeal Carcinoma with Radiologic Imaging

The 7th edition of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) TNM classification for NPC is currently the most commonly used staging system internationally (Table 11.1). It is based purely on the anatomical spread of both the primary tumor and the metastatic nodes, without taking into account the size of the tumor or its histologic grade. Significant stage migration has been observed over time with the advances in imaging technology and treatment modalities. Magnetic resonance imaging (MRI) has generally replaced computerized tomography (CT) for local tumor staging because it provides better soft tissue resolution. MRI also plays an important role in RT treatment planning because it provides more accurate delineation of tumor target. For the staging of M stage, studies do not support the routine use of CT thorax, bone scan, or abdominal ultrasonography in average-risk patients because of the low positive detection rate for metastases, and such imaging is usually reserved for patients at high risk of distant metastasis.[10–13]

Table 11.1 The 7th Edition of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) TNM Classification for NPC

T Stage	N Stage
T1: Nasopharynx, oropharynx, or nasal fossa T2: Parapharyngeal extension T3: Bony structures, paranasal sinuses T4: Intracranial extension, cranial nerve, hypopharynx, orbit, infratemporal fossa(masticatory space)	N0: None N1: Unilateral cervical or retropharyngeal (irrespective of laterality), <6 cm, above supraclavicular fossa N2: Bilateral cervical node, <6 cm, above supraclavicular fossa N3a: >6 cm N3b: In supraclavicular fossa
M Stage	**Overall Stage**
M0: No distant metastasis M1: Distant metastasis is present.	I: T1 N0 M0 II: T1 N1 M0, T2 N0–1 M0 III: T1/2 N2 M0, T3 N0–2 M0 IVA: T4 N0–2 M0 IVB: Any T, N3, M0 IVC: Any T, any N, M1

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^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET)-CT has become increasingly popular in staging and as a tool to detect tumor persistence or recurrence. Several studies have compared the accuracy of PET-CT and MRI in detecting primary tumor, retropharyngeal nodes,

cervical nodes, and distant metastasis, but their results are inconsistent.[14]–[17] In the larger study by Ng et al.,[17] MRI appears to be superior for assessing the primary tumor and retropharyngeal nodes, whereas PET-CT is more accurate than MRI for detecting cervical nodal metastasis and more accurate than CT and bone scans for detecting distant metastasis. A recent meta-analysis of eight series has confirmed the reliable performance of PET or PET-CT in the evaluation of distant metastasis, with a pooled sensitivity of 83% and specificity of 97%.[18]

Early detection of local recurrence is crucial to successful salvage. However, it is notoriously difficult to diagnose submucosal or deep-seated recurrence by endoscopy alone, and MRI or CT is unable to distinguish post-RT scarring or inflammation from genuine recurrence.[19] Controversy remains as to the superiority of PET-CT over MRI on this aspect. In a systematic review of 21 articles, Liu et al.[20] suggested that PET was the best modality for diagnosis of local residual or recurrent NPC. In the foreseeable future, PET-CT is going to play a more important role in the staging of NPC at diagnosis and at recurrence and in the monitoring of treatment response.

Primary Treatment for Nonmetastatic Nasopharyngeal Carcinoma

Two-Dimensional Radiotherapy

External RT has been the mainstay treatment for nonmetastatic NPC since the introduction of megavoltage machines in the mid-1960s, when the OS was only 25% at 5 years. With improvement in simple two- to three-field arrangements delivering 60 to 70 Gy of two-dimensional RT (2DRT) to the nasopharynx and its regional lymphatics, the OS rate was typically in the order of 50% during the 1970s to 1980s, with the rate of locoregional failure over 25%.[21]–[23] The major drawback of 2DRT is the unnecessary irradiation of abundant normal tissues, and any attempt at vital organ sparing would inevitably compromise target coverage.[24] Further improvement of treatment

outcome was seen in the 1990s, and this occurred as a result of advances in diagnostic imaging and the use of more aggressive strategies such as RT dose escalation and chemotherapy. In a retrospective analysis on 2,687 patients treated during 1996 to 2000s, the OS rate was 75% and local failure-free rate was 85% at 5 years.[1]

Three-Dimensional Conformal Radiotherapy

The transition from 2DRT to three-dimensional conformal radiotherapy (3DCRT) marked a great advance in RT development in the late 1990s, and the development of computer planning system and multileaf collimator is a representative achievements during this period. The integration of CT or MRI images into the 3D treatment planning system provides more accurate spatial information on the tumor target and normal organs, which in turn enables a more flexible adjustment of the beam directions. The use of multileaf collimator allows better shaping of beam aperture that conforms to the shape of the target and avoids vital organs in the vicinity. The dosimetric advantage of 3DRT has been translated into significant improvement in patient survival as well as reduction in serious toxicities.[4]

Intensity-modulated Radiotherapy

The use of 3DCRT was rapidly overtaken by the introduction of intensity-modulated radiotherapy (IMRT), in the late 1990s. IMRT is an advanced form of 3DCRT with additional capacity to modulate beam intensity pixel by pixel across the treatment field. Working in conjunction with the inverse planning computer optimization algorithm, an optimized fluence can be obtained according to the dose–volume constraints set by the physician. It is particularly useful in generating a concave-shaped dose distribution with steep dose-gradient around the brainstem, spinal cord, and optic pathway. The principal benefit of IMRT in early-stage NPC is the sparing of the parotid glands. In locoregionally advanced NPC, IMRT offers better tumor coverage and protection of critical neurologic organs and allows room for dose escalation.[25–27] Moreover, IMRT permits the delivery of different dose intensities to different targets according to their clinical risks and enables biologic enhancement through the concept of simultaneous integrated boost (SIB) technique. A comparison of dose distribution between 2DRT and IMRT is demonstrated in Figure 11.1.

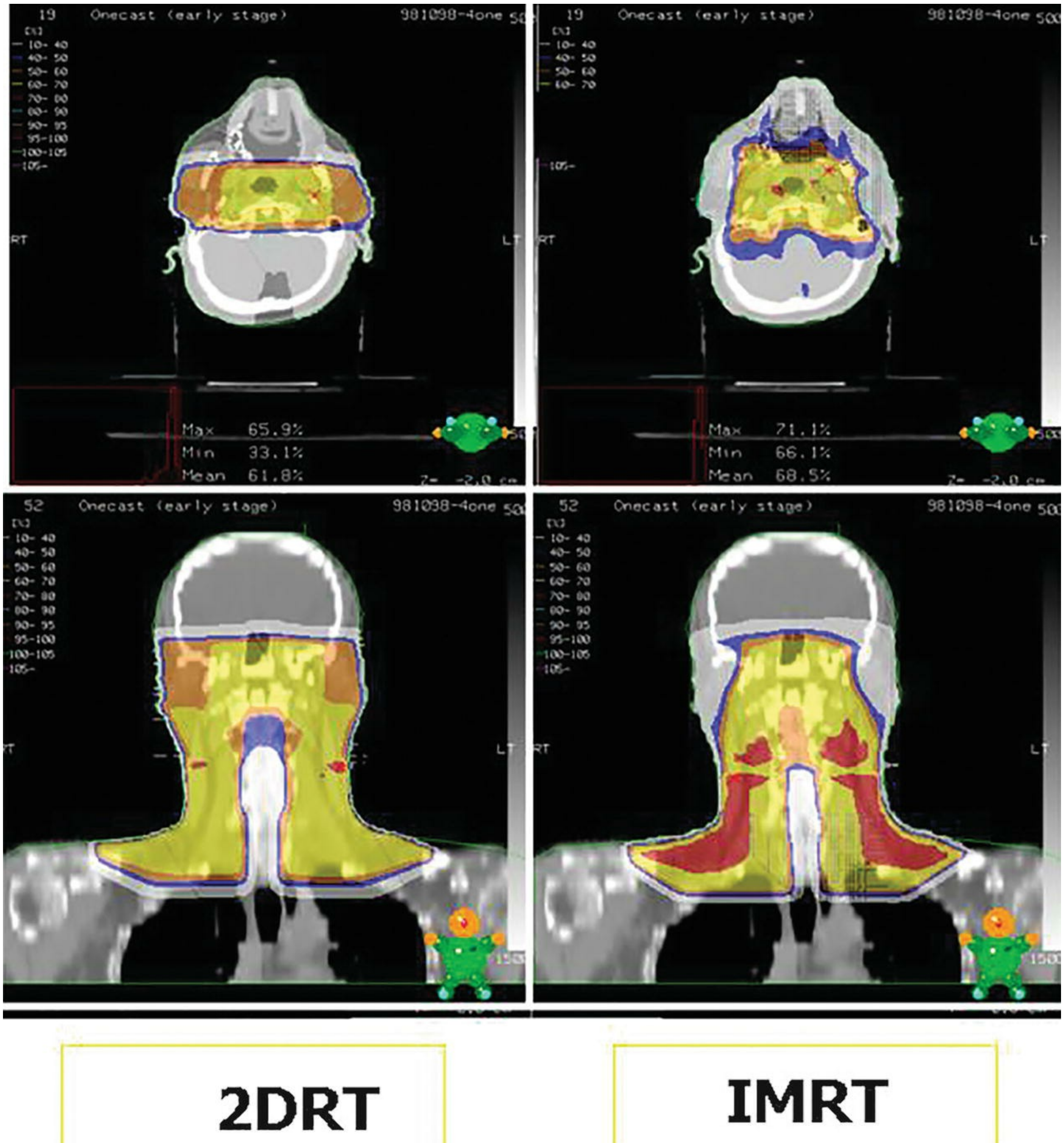

Figure 11.1. Comparison of isodose distribution between 2DRT and IMRT.

This dosimetric advantage has been translated into better local control rate as reported in many retrospective series[28]–[45] (Table 11.2). In addition, three randomized studies comparing IMRT versus 2DRT have been reported thus far. In early-stage NPC, Kam et al. and Pow et al. both confirmed that IMRT results in significantly better recovery of parotid salivary function than

2DRT.[49,50] Peng et al.[51] randomized patients to 2DRT or IMRT and found a significant improvement in 5-year local control rate (91% vs. 84%, $p = 0.046$) and OS (80% vs. 67%, $p = 0.001$) and significant reduction in late toxicities including cranial neuropathy, temporal lobe necrosis, xerostomia, trismus, and fibrosis of the neck. However, several controversies in IMRT remain unresolved. It is uncertain whether IMRT is superior to 3DCRT in terms of patient's outcome. Fang et al.[37] and Lee et al.[4] did not observe significant differences in locoregional control, OS, or toxicities between IMRT and 3DCRT. The suboptimal local control rate in locally advanced NPC patients, and the tangible figures on some severe RT complications are really too significant to be ignored.[29] The optimal total dose level and time–dose–fractionation schedule are still unclear, because several RT acceleration or dose escalation strategies (such as SIB technique, or sequential boost) have not been formally compared in randomized studies. Another outstanding issue is the need to validate and standardize the definition of clinical target volume (CTV). This is important because the therapeutic window of RT in NPC is narrow, and tailoring of treatment volume is essential to avoiding inadequate or futile treatment margins. Despite all these uncertainties as mentioned, IMRT is rapidly becoming a contemporary standard of care for the treatment of NPC worldwide.

Table 11.2 Results of Studies on the Treatment of NPC with IMRT

Study	*N*	Stage T3–T4 (%)	Median Follow-Up (mo)	Total Dose (Gy)	Dose/ Fraction (Gy)	Time Point (y)	Local Control (%)	Nodal Control (%)	Distant Control (%)	Overall Survival (%)
Lee[39]	118	41	30	70	2.12	4	96	98	72	74
Kam[46]	63	51	29	66	2	3	92	98	79	90
Wolden[47]	74	53	35	70.2	2.34	3	91	93	78	83
Kwong[43]	50	0	14	70	2	3	100	92.3	100	100
Kwong[42]	50	100	25	76	2.17	2	96[a]	NR	94	92
Lin[44]	326	61	33	62.6–69.75	2.2–2.25	3	95	98	90	90
Lee[45]	20	40	27	72	2.4	2	88[a]	NR	90	NR
Koom[30]	24	29	26	64.8	2.4	3	93	87	88	96
Fang[37]	110	24.5	40	72	2.4	3	84.2[a]	NR	82.6	85.4
Tham[36]	195	NR	37	70	2.12	3	89.6[a]	NR	89.2	94.3
RTOG 0225[48]	68	34	31	70	2.12	2	92.6	90.8	84.7	80.2
Wong[38]	175	35	34	70	2.12	3	93.6	93.3	86.6	87.2
Ng[35]	193	61	30	70	2–2.12	2	95	96	90	92
Bakst[34]	25	28	33	70.2	2.34	3	91	91	91	89
Xiao[33]	81	100	54	68	2.27	5	94.9	NR	NR	74.5
Lai[32]	512	52	52.8	NR	2.27	5	93	97	84	NR

[a]Locoregional control.

NR, not reported; y, years; mo, months.

Dose Escalation

The dose–response effect in NPC has been well established. Lee et al.[52] showed that risk of local failure was found to be decreased by a factor of 9% per additional Gy. The value of dose escalation after a basic course of 66 to 70 Gy large-field 2DRT has also been demonstrated by a retrospective review from the Hong Kong NPC Study Group on 2,462 patients, of whom 65% received brachytherapy, 2DRT, 3DRT, or stereotactic RT (SRT) boost.[53] The use of RT boost in patients with T1 to T2a and T3 to T4 disease was a significant determinant of local control. The commonly agreed standard total dose should be more than or equal to 70 Gy at 2 Gy fraction per day. The achievable total dose is limited by the tolerance of the surrounding normal critical organs, in particular, the temporal lobe.[54] Several techniques have been studied to achieve a total dose beyond 66 to 70 Gy, which include brachytherapy boost or 3DRT/IMRT/SRT boost after the conventional fractionation RT and the SIB technique in the IMRT era.

Brachytherapy Boost

Studies from Hong Kong have shown that the use of two to three fractions of brachytherapy could significantly enhance local control in early T-stage disease.[55,56] The indication of the brachytherapy boost is currently confined to the treatment of early T-stage disease due to its limited dose penetration. Because distant failure is the dominant mode of failure in more advanced disease, the role of brachytherapy boost is questionable. Levendag et al.[57] reviewed 411 patients with advanced NPC (T1 or T2 with nodal metastases, or T3 or T4 and node-negative disease), of whom 50% of patients received brachytherapy boost of 11Gy. A significant reduction in local failure was observed in the early T-stage subgroup (0% vs. 14%, $p = 0.023$), but not in the advanced T-stage group.[57] Rosenblatt et al.[58] randomized 274 patients with stage III and nonmetastatic stage IV NPC to chemoradiotherapy with or without brachytherapy boost thereafter. The 3-year local recurrence-free survival was not significantly improved in either the whole T-stage or the early T-stage group.[58]

Sequential Conformal/IMRT/Stereotactic Boost

SRT boost has been investigated by the Stanford University (USA) and Taiwan groups, who used CyberKnife or linear accelerator-based technologies to treat NPC patients following radical 2DRT or IMRT.[59,60] A high control rate in T4 disease was also observed, but the Stanford series reported a temporal lobe necrosis rate of 12% in the entire group and 11% among IMRT-treated patients.[60] In response, the investigators have now decreased their SRT dose to 8 Gy in single fraction or 12 Gy in 3 fractions, whereas the total dose to the temporal lobes is kept below a maximum total dose of 55 to 60 Gy. The long-term safety of this approach and its impact on the therapeutic ratio are yet to be established. In the report by Kam et al.[46], 63 patients were treated with 66 Gy to the gross tumor volume (GTV) using IMRT, and dose escalation was performed in 36% of patients with T2b to T4 disease via IMRT or stereotactic plan (8 Gy in 4 fractions). In this study, dose escalation was found to be a favorable prognostic factor for progression-free and distant metastases-free survival, and the incidence of temporal lobe necrosis was 3%. In a retrospective analysis by Lee et al.[61] on patients who were irradiated with a 3D conformal technique (2 Gy/fraction/day to 70 Gy), 8.3% temporal lobe necrosis rate was detected at 5 years among patients who received fractionated SRT boost. In summary, although there is strong evidence of a dose–response relationship above 66 to 70 Gy, the impact on local control is more obvious after 2DRT and less compelling with IMRT. Caution must be taken to optimize the target conformity, dose heterogeneity, and dose spillage to the neurovascular structures. As IMRT is capable of pushing the therapeutic ratio further owing to its steep dose gradient, the demand for a meticulous design of margin requirement and thus the higher dependence on the setup accuracy cannot be overemphasized.

Simultaneous Integrated Boost in IMRT

SIB, also called simultaneous modulated and accelerated RT (SMART), exploited the “dose-painting” capacity of IMRT by delivering different dose levels to different regions according to the level of risk. This allows a “once-a-day” fractionation schedule with selective dose acceleration to different tumor targets without undue damage to normal organs. Consequently, a higher biologically equivalent dose can be delivered to the gross tumor than

the microscopic disease. A number of studies have evaluated SIB in NPC with a nominal total dose of 64.8 to 76 Gy to the GTV in 2.12 to 2.4 Gy/fraction over 27 to 35 fractions.[30,34,36–39,42,44,45,47,48] Despite the variation in SIB dose fractionation across these studies, the local or locoregional control rate was 88% to 96% after 2 to 5 years of follow-up. However, the incidence of severe late toxicities remains a concern. Bakst et al.[34] reported 12% temporal lobe necrosis rate, whereas Kwong et al.[42] reported moderate to severe hearing impairment in 42% and carotid pseudoaneurysm in 4% of patients.

Other centers used a “mini-SIB” schedule with a lower fraction size. The Radiation Therapy Oncology Group (RTOG) 0225 multicenter phase II study examined a schedule of 70 Gy per 33 fractions in 2.12 Gy/fraction and reported a 2-year local progression-free survival (PFS) of 92.6% and regional PFS of 90.8%.[48] The “mini-SIB” schedule has been tested in a phase III randomized study by Peng et al.[51] who compared IMRT (70 Gy at 33 fractions) with 2DRT in 616 NPC patients. The IMRT arm was associated with a significant improvement in locoregional control and OS and reduction in the incidence of hearing impairment, late xerostomia, temporal lobe neuropathy, trismus, and neck fibrosis. For T4 disease in particular, the use of “mini-SIB” (<2.12 Gy/fraction) or conventional 2 Gy per fraction in combination with chemotherapy may be safer without significantly compromising tumor control if the temporal lobes are kept below 65 Gy.[31]

Incorporation of Chemotherapy in the Treatment of Locoregionally Advanced Nasopharyngeal Carcinoma

Background

Because distant metastasis is the main cause of treatment failure following RT, over a decade of research has been devoted to the intensification of

treatment for locoregionally advanced NPC by incorporating adjunctive chemotherapy. To date, at least seven meta-analyses have concluded that the addition of chemotherapy during RT (at any time point) confers a survival advantage over conventional RT alone in patients with locoregionally advanced (i.e., stage III to IVB) NPC.[62–66] Of these studies, only the one by Baujat et al.[64] was based on patient-derived data, whereas the rest were based on published data. Several observations can be made from these analyses as outlined in Table 11.3.[62–68] The use of concurrent chemotherapy will lead to a 26% to 52% reduction in the risk of death, which amounts to an absolute OS benefit of around 20% after 5 years.[63,64] This benefit has been associated with improvement in locoregional and distant recurrence rates.[63,64] Of the three sequences of chemotherapy that were evaluated—induction, concurrent, and adjuvant chemotherapy, concurrent chemotherapy is by far most consistently associated with the largest magnitude of improvement in OS and PFS than other sequences.[63,64]

Table 11.3 Meta-Analyses on the Benefit of Adjunctive Chemotherapy During Radiotherapy for Patients with Locoregionally Advanced NPC

Author	Year	No. of RCT (Patients)	Result
Huncharek and Kupelnick[62]	2002	6 RCT (1,500)	*CRT (any sequence) vs. RT alone:* DFS 3 y: OR = **0.60** (95% CI, 0.49–0.73) OS 3 y: OR = 0.81 (95% CI = 0.66–1.00)
Langendijk et al.[63]	2004	10 RCT (2,450)	*CRT (any sequence) vs. RT alone:* OS: HR = **0.82** (95% CI, 0.71–0.95, *p* = 0.01) *Chemo lowers risk of*: LRR: RR = **0.47** (95% CI, 0.33–0.67) DMR: RR = **0.72** (95% CI, 0.62–0.84) *Concurrent*: HR = **0.48** (95% CI, 0.32–0.72) *Neoadjuvant:* HR = 0.87 (95% CI, 0.72–1.04) *Adjuvant:* HR = 0.99 (95% CI, 0.71–1.36)
Baujat et al.[64]	2006	8 RCT (1,753)	*CRT (any sequence) vs. RT alone:* OS: HR = **0.82** (95% CI, 0.71–0.94; *p* = 0.006) DFS:HR = **0.76** (95% CI, 0.67–0.86; *p* < 0.0001) *Chemo lowers risk of*: LRF: HR = **0.76** (95% CI, 0.64–0.91) DF: HR = **0.72** (95% CI, 0.59–0.87) *Concurrent*: HR = **0.60**; 95% CI, 0.48–0.76 *Induction*: HR = 0.99; 95% CI, 0.80–1.21 *Adjuvant*: HR = 0.97; 95% CI, 0.69–1.38
Zhang et al.[67]	2010	7 RCT (1,608)	*Concurrent vs. RT alone:* 5 y OS: RR = **0.74** (95% CI, 0.62–0.89) 5 y LRF: RR = **0.67** (95% CI, 0.49–0.91) 5 y DR: RR = **0.71** (95% CI, 0.58–0.88)
Liang et al.[68]	2012	11 (RCT) 1,096	*Induction chemo vs. RT alone:* OS: RR = 0.99 (95% CI 0.72–1.36) PFS: **RR = 0.37** (95%CI 0.20–0.69) LRF: 1.08 (95% CI 0.84–1.38) DF: 0.98 (95% CI 0.75–1.27)
Liang et al.[65]	2012	5 RCT (793)	*Adjuvant chemo vs. CRT alone*: OS = 1.02 (95% CI 0.89–1.15) FFS = 0.93 (95% CI 0.72–1.21) LRF = 1.07 (95% CI 0.87–1.32) DF = 0.95 (95% CI 0.80–1.13)
Ouyang et al.[66]	2012	6 RCT (1,418)	*Neoadjuvant chemo*: HR = **0.82** (95% CI = 0.69–0.98, *p* = 0.03) DMR: RR = **0.69** (95% CI 0.56–0.84, *p* = 0.0002) *Adjuvant chemo*: OS: HR = 1.04 (95% CI 0.79–1.37) LRR: RR = **0.71** (95% CI 0.53–0.96)

RR, risk ratio; CRT, adjunctive chemotherapy during radiotherapy; FFS, failure-free survival; PFS, progression-free survival; LRF, locoregional failure-free survival; DF, distant failure-free survival; RCT, randomized trial; chemo, chemotherapy; DMR, distant metastasis rate; LRR, locoregional recurrence rate; HR, hazard ratio.

Concurrent Chemoradiotherapy

The US Intergroup study was the first to demonstrate a survival advantage of adding concurrent cisplatin-based chemotherapy to RT over RT alone in a multicenter randomized study of patients most of whom had locoregionally advanced NPC.[69] In this study, 147 patients with nonmetastatic stage III to IV NPC were randomized to either RT alone or RT with three cycles of concurrent cisplatin followed by three cycles of adjuvant cisplatin and 5-flurouracil (5FU). Unlike NPC from endemic regions where nearly all of the

cases were of the WHO type II and III histologic subtypes, around 20% of patients enrolled in this study had WHO type I (squamous) form of NPC. At a median follow-up of 2.7 years, the RT alone arm was associated with a hazard ratio (HR) of 4.34 (95% confidence interval, CI, 2.47 to 7.69) for progression and/or death and an HR of 2.50 (95% CI, 1.29 to 4.84) for death compared with the combined arm (Table 11.4).[81–85] This landmark study did not immediately change clinical practice in Asia, as Asian investigators were eager to validate their result in local population where nearly all NPC were of the WHO type II to III histologic subtypes. Several multicenter randomized studies have been published since 2002 (Table 11.4).[69–80] Six of the eight selected studies showed an OS advantage at 5 years,[69,71,75,79,86] with HRs of 0.51 at 3 years[75] and 0.54 to 0.71 at 5 years.[71,79,80] Of the six positive studies outlined in Table 11.4, a variety of concurrent chemotherapy regimens were used, which included a weekly schedule of low-dose cisplatin,[71,79,80] 3-weekly high-dose cisplatin,[69,75] and a two-drug regimen such as cisplatin–FU.[86] The total doses of RT delivered in these studies were between 66 and 74 Gy (Table 11.4).[71,79,86] In the phase III study by Chan et al.,[71,72] which used weekly concurrent cisplatin during RT, the HR was 0.71 (p = 0.049) favoring the concurrent arm for the entire group of patients with stage II to IVB NPC, whereas the magnitude of benefit for the T3 to T4 subgroup was higher with an HR of 0.51 (95% CI = 0.3 to 0.87, p = 0.013). Some of the studies found an association between OS benefit with improvement in distant metastasis or with failure-free survival, thus further adding weight to the hypothesis that chemotherapy may improve survival by controlling micrometastases.[75,79,86]

Table 11.4 Summary of Key Phase III Studies Comparing Concurrent Chemoradiotherapy Versus Radiotherapy Alone

Author	Year	TNM Stage%	*N*	Treatment Arms	Result (All Stages)			
						CRT%	RT%	*p*-value
Al-Sarraf et al.[69,70]	1998 (2001)	III: 9 IV: 91	147	RT alone (70 Gy) Cis(3 wkly)–RT → cis–FU	5 y OS 5 y PFS	67 58	37 29	**0.001** **0.001**
Chan et al.[71,72]	2002 (2005)	II: 28.8 III:29.4 IV:41.8	350	RT alone (66 Gy) Cis(wkly)–RT	5 y OS 5 y PFS	72 62	59 52	**0.048** 0.076
					5 y HR (OS) = **0.71** (95% CI 0.5–1.0), *p* = 0.049 5 y HR (PFS) = 0.74 (95% CI 0.54–1.0), *p* = 0.06			
Lin et al.[73]	2003	III:19.7 IV:80.3	284	RT alone (70–74 Gy) Cis(4 wkly)–FU–RT	5 y OS 5 y PFS 5 y DF	72.3 71.6 78.7	54.2 53.0 69.9	**0.002** **0.001** 0.057
Kwong et al.[74]	2004	(Ho's) II:3 III:88 IV:9	219	RT alone (62.5–68 Gy) RT → adjuv chemo CRT CRT → adjuv chemo	3 y OS 3 y FFS 3 y DMR	86.5 69.3 29.4	76.8 57.8 14.8	0.06 0.14 **0.026**
					HR (OS, CRT) = **0.41**; 95% CI, 0.21–0.78 HR (FFS, CRT) = 0.65; 95% CI, 0.41–1.03			
Wee et al.[75]	2005	II:1 III:45 IV:54	221	RT alone (70 Gy) Cis(3 wkly)–RT → cis–FU	3 y OS 3 y DFS 2 y DF	80 72 30	65 53 13	**0.0061** **0.0093** **0.0029**
					3 y HR (DFS) = **0.57** (95% CI, 0.38–0.87; *p* = 0.01) 3 y HR (OS) = **0.51** (95% CI, 0.31–0.81; *p* = 0.006)			
Lee et al. (NPC9901 study)[76,77]	2005 (2011)	III:61 IV:39	348	RT alone (>66 Gy) Cis(3 wkly)–RT → cis–FU	5 y OS 5 y FFS 5 y LRF 5 y DF	68 67 88 74	64 55 78 68	0.81 **0.014** **0.005** 0.32
					5 y HR (OS) = 0.81 (95% CI = 0.58–1.13) 5 y HR (PFS) = **0.72**, (95% CI = 0.53–0.98)			
Zhang et al.[78,79]	2005 (2013)		115	RT alone (70–74 Gy) Oxaliplatin–RT	5 y OS 5 y MFS	73.2% 74.3%	60.2% 63%	**0.03** **0.03**
Chen et al.[80]	2013	III: 36 IV: 64	316	RT alone (66 Gy) Cis (wkly)–RT → cis–FU	5 y OS 5 y PFS	72 68	62 57	**0.043** **0.015**
					5 y HR (OS) = **0.69** (95% CI: 0.48–0.99, *p* = 0.043)			

adjuv, adjuvant; chemo, chemotherapy; HR, hazard ratio for death for concurrent chemoradiotherapy over RT alone; CRT, concurrent chemoradiotherapy; RT, radiotherapy; OS, overall survival; DFS, disease-free survival; FFS, failure-free survival; RFS, relapse-free survival; CI, confidence interval; MFS, metastasis-free survival; wkly, weekly.

Toxicities and Treatment Compliance

Table 11.5 outlines the acute toxicities and compliance to concurrent and/or adjuvant chemotherapy in the phase III clinical trials. Although different criteria were used to report toxicities and different RT planning techniques were used by these studies, the types of moderate to severe (grade 3 to 4) toxicities that are more commonly encountered with concurrent chemotherapy were oropharyngeal mucositis and neutropenia, followed by emesis and RT-related skin reaction. Neutropenic fever and treatment-related deaths were not commonly encountered (where reported).[77] Taking into

account that these studies were published before IMRT was commonly used, the rate of grade 3 to 4 mucositis would generally be increased by 10% to 20% with the addition of concurrent chemotherapy (Table 11.5).

Table 11.5 Toxicities of Selected Phase III Studies of Concurrent Chemoradiotherapy Versus Conventional RT (Non-IMRT)

Author	Treatment Arms (Criteria)	Gr 3 and/or 4 (Criteria)	CRT% of Patients	RT%
Al-Sarraf et al.[69,70]	RT (70 Gy) Cis(3 wkly)–RT → cis–FU	(SWOG) Mucositis RT skin Leukopenia	 37 2 29.4	 28 4 <1
		63% completed concurrent chemo 55% completed adjuvant chemo		
Chan et al.[71,72]	RT alone Cis(wkly)–RT	(WHO) Mucositis RT skin Leukopenia	 48.9 – 12.6	 35.8 – 0
		44% had six cycles concurrent chemo 60% had five cycles concurrent chemo		
Lin et al.[73]	RT alone Cis(4 wkly)–FU–RT	(WHO) Mucositis RT skin Leukopenia	 45.4 30 4.3	 30 25.9 0
Kwong et al.[74]	RT alone RT → adjuv chemo CRT CRT → adjuv chemo	(RTOG) Mucositis RT skin Leukopenia	 46.4 21.8 3.6	 24.8 10.1 0
Wee et al.[75]	RT alone Cis(3 wkly)–RT → cis–FU	(RTOG) Mucositis RT skin Leukopenia	 48.1 4.7 14.2	 31.8 4.7 0
		71% had all concurrent chemo 68.5% had all adjuvant chemo		
Lee et al. (NPC9901 study)[76,77]	RT alone Cis(3 wkly)–RT → cis–FU	(RTOG) Mucositis RT skin Leukopenia	 62 20 32	 48 16 1
		65% had all six cycles of chemo		
Zhang et al.[78,79]	RT alone Oxaliplatin–RT	(WHO) Mucositis RT skin Leukopenia	 10 9 <1	 5 25.4 0
		97% had concurrent chemo		
Chen[80]	RT alone Cis(wkly)–RT cis–FU	(WHO) Mucositis RT skin Leukopenia	 45 4 23	 35 3 0

WHO, World Health Organization; RTOG, Radiation Therapy Oncology Group; CRT, concurrent chemoradiotherapy; RT, radiotherapy; Adjuv, adjuvant; chemo, chemotherapy.

Compliance to concurrent chemotherapy in the phase III studies as outlined

in Table 11.5 was mixed, with the rates of completion of planned chemotherapy reported to be around 45% to 90% (Table 11.5). The number of cycles of cisplatin delivered during RT has been shown to be a prognostic factor in some retrospective analyses.[87–89] Lee et al.[89] showed that patients who received three or more cycles of high-dose cisplatin during RT were more likely to derive OS benefit than were those who did not.

Some studies have compared the incidence of late toxicities (beyond 3 years) associated with concurrent chemoradiotherapy. In a phase III study that compared conventional fractionated RT with or without high-dose cisplatin, the 3-year actuarial rate of late toxicities was higher in the concurrent arm than the RT alone arm (28% vs. 13%, $p = 0.024$; HR = 1.87; 95% CI, 1.08 to 3.26). The most common grade 3 to 4 late toxicities in the concurrent arm were hearing loss (21%), endocrine dysfunction (8%), and peripheral neuropathy (2%).[76] In another study, which compared conventional versus hyperfractionated RT with or without concurrent chemotherapy, the 3-year actuarial rates in the RT and concurrent arm were, respectively, 14% versus 31% for all late toxicities, 9.5% versus 15.7% for grade 3 to 4 hearing loss, and 0% versus 2% for grade 3 to 4 RT-related skin fibrosis.[90] Chen et al.[80,91] found that patients treated with concurrent chemoradiotherapy experienced a greater incidence of grade 3 to 4 hearing loss (28% vs. 18%, $p = 0.048$), cranial neuropathy (10% vs. 4%, $p = 0.042$), and peripheral neuropathy (2% vs. 0, $p = 0.041$) than RT alone. The incidence of serious brainstem damage, myelitis, and RT-related secondary malignancies was uncommon (1% to 3%).[76,80]

Several studies have reported the incidence of acute and late toxicities of adding concurrent chemotherapy to IMRT.[33,40,46–48,92] In a study by Wolden et al. in which 65% of patients received concurrent chemotherapy during IMRT, 41.2% of patients experienced grade 3 to 4 acute mucositis, 7% had grade 3 hearing loss, and 4% had grade 3 dysphagia 4%.[47] In a study by Wang et al.,[92] which included 300 patients with stage III to IVB NPC who received concurrent cisplatin–RT, grade 3 acute mucositis, dermatitis, and xerostomia were observed in 33.3%, 4.0%, and 4.7% of patients, respectively. At 24 months, grade 2 xerostomia (no grade 3) occurred in 12.3% and grade 3 hearing loss in 0.4% of patients. In a study from Hong Kong, in which over 80% of 1,593 patients with stage III to IV NPC received concurrent cisplatin during IMRT, the risk of hearing impairment was higher

(HR = 1.56) with the addition of cisplatin. The risk of temporal lobe necrosis and cranial neuropathy were not increased.[4] Overall, these studies suggest that the addition of cisplatin to IMRT is safe with acceptable rates of grade 3 to 4 acute and late toxicities.

Induction Chemotherapy

Successive generations of phase II single-arm studies on induction chemotherapy have reported high tumor response rates with platinum-based doublets or triplets and promising early survival rates.[93–95] Despite the initial promise, subsequent randomized studies have failed to demonstrate an OS benefit of induction chemotherapy versus conventional RT alone (Table 11.6).[81–85] Using concurrent chemoradiotherapy as a strategic framework in the treatment of locoregionally advanced NPC, numerous phase II studies have reported their experience with adding induction chemotherapy to chemoradiotherapy throughout the 2000s.[94–103] Despite the heterogeneous nature of these studies in terms of the number of cycles and types of chemotherapy used, studies that employed platinum-based drug triplets reported impressive tumor response rates of 86% to 100% and 3-year OS rates between 88% and 94.8%.[94,95,99,103] For the studies using drug doublets, the overall response rates (79% to 100%) and 3-year OS rates (80% to 91.8%) were reported.[96–98,100–102] At the Prince of Wales Hospital (Hong Kong), concurrent chemoradiotherapy alone was compared with induction chemotherapy followed by chemoradiotherapy in a randomized phase II trial of 65 patients with stage III to IV NPC.[104] Although the study was not powered to detect a difference in survival between the two arms, a significant reduction in the risk of death (HR = 0.17; 95% CI = 0.037 to 0.82; $p = 0.013$) and a 17% absolute improvement in 2-year OS was found.[104] A subsequently published meta-analysis by Ouyang et al.[66] found that the addition of induction chemotherapy was associated with a modest absolute OS benefit of 5.13% at 3 years. To address the question of whether induction chemotherapy adds benefit to concurrent chemoradiotherapy, several phase III studies are now being conducted across Asia, Europe, and North Africa (National Cancer Institute trial numbers: NCT00997906, NCT00201396, NCT00828386, NCT01245959, NCT00379262). A Singaporean group has recently presented their result in abstract form. Tan et al.[105] randomized 180 patients with stage III to IVB NPC to concurrent weekly cisplatin–RT with or

without three cycles of induction chemotherapy with a triplet regimen consisting of cisplatin, paclitaxel, and gemcitabine. This study was powered to detect a 15% difference in OS, and at a median follow-up of around 3 years, no significant difference in OS between the two arms was found. In another recently published study of 803 patients with stage III to IVB from Hong Kong, which consisted of six different treatment arms, preliminary analyses have failed to show that the addition of induction cisplatin–capecitabine could improve the primary endpoint of PFS.[106] The results of other studies are eagerly awaited.

Table 11.6 Phase III Studies Comparing Induction Chemotherapy with RT Alone or Chemoradiotherapy

First Author	Year	*N*	Patients	Arms	Result (All Stage)			
						RT%	CRT%	*p-value*
Chan[81]	1995	82	II–IVB	Cis-5FU × 2 → RT → Cis-5FU × 4	*2 y OS* *2 y DFS*	81 72	80 68	*NS* *NS*
Roussy[82]	1996	339	II–IVB	RT BEP × 3 → RT	*5 y OS* *5 y DFS*	46 30	40 40	*NS* *0.01*
Chua[83]	1998	334	II–IVB	RT EC → RT	*3 y OS* *3 y RFS*	42 71	48 78	*NS* *NS*
Ma[84]	2001	456	II–IVB	RT CBF → RT	*5 y OS* *5 y FFS*	56 49	63 59	*NS* *0.05*
Hareyama[85]	2002	80	I–IVB (>70% III–IV)	RT Cis-5FU × 2 → RT	*5 y OS* *5 y DFS*	48 43	60 55	*NS* *NS*

All are intention-to-treated data.

BEP, bleomycin, epirubicin, cisplatin; EC, cisplatin, epirubicin; CBF, cisplatin, bleomycin, 5-fluorouracil; OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; FFS, failure-free survival; CRT, concurrent chemoradiotherapy.

Adjuvant Chemotherapy

Phase III studies comparing RT alone versus RT and adjuvant chemotherapy have failed to find a survival benefit with the addition of adjuvant chemotherapy in patients with locoregionally advanced NPC (Table 11.7).[74,107–109] In the largest multicenter study published to date, over 500 patients with stage III to IVB NPC from China were randomized to concurrent chemoradiotherapy with or without adjuvant chemotherapy with failure-free survival being the primary endpoint.[109] Compliance to chemotherapy was comparable with historic rates from other phase III studies

(see Table 11.4), with 63% of patients completing all planned chemotherapy.[109] This study did not identify a statistically significant difference in failure-free survival in the intention-to-treat population or in any patient subgroups. However, the 2-year follow-up period is relatively short and only 63% of patients could complete the planned chemotherapy. For patients who have been identified to be at higher risk of disease recurrence using prognostic biomarker such as plasma EBV DNA, the significance of adjuvant chemotherapy is being investigated as will be discussed below.

Table 11.7 Selected Phase III Studies that Compared RT Alone Versus Adjuvant Chemotherapy

First Author	Year	*N*	Patients	Arms	Result (All Stage)			
						RT%	RT-C%	*p-value*
Rossi[107]	1988	229	II–IV	RT RT → VAC × 6	*2 y* *OS* *RFS*	 55.8 67.3	 57.7 58.3	 *NS* *NS*
Chi[108]	2002	157	IV	RT RT → PFL × 9	*5 y* OS RFS	 60.5 49.5	 54.5 54.4	 *NS* *NS*
Chen[109]	2011	508	III–IV (exclude N0 pts)	Cisplatin–RT Cisplatin–RT → cisplatin–5FU × 3	*2 y* OS DFS	 94 88	 92 86	 *NS* *NS*

VAC, vincristine, cyclophosphamide, and adriamycin; PFL, weekly cisplatin, 5-fluorouracil-leucovorin; RFS, relapse-free survival; OS, overall survival; RT, radiotherapy; C, chemotherapy; 5FU, 5-fluorouracil; DFS, disease-free survival.

Stage II Nasopharyngeal Carcinoma—Concurrent Chemoradiotherapy or Not?

In the largest retrospective study of over 2,600 patients in Hong Kong, ~41% of patients had stage II NPC at diagnosis with a 5-year OS of 84% and PFS of 73% following treatment with mainly RT alone.[1] Approximately 13% of patients with stage II NPC develop distant metastasis within 5 years from RT.[1] Some investigators have proposed the use of adjunctive chemotherapy during RT for patients with stage II disease. Subgroup analysis of stage II cohorts in several phase III clinical trials have yielded mixed results.[71,110] In the largest phase III study reported to date from China,[87] 236 patients with stage II NPC were randomized to either RT alone or RT plus weekly

cisplatin. The Chinese 1992 staging system was used in this study where stage II NPC was defined via MRI and clinical examination. Translating these into the AJCC criteria, this meant that around 10% to 16% of subjects actually had stage III NPC in this study. At a median follow-up of 60 months, the addition of concurrent cisplatin to RT significantly improved the 5-year OS rate with an HR of 0.30 (95% CI = 0.12 to 0.76; $p = 0.007$) and the 5-year PFS with an HR of 0.45 (95% CI = 0.23 to 0.88; $p = 0.017$).[87] The magnitude of benefit reported seemed larger than what has been reported for patients with stage III to IV NPC (Table 11.4), despite the fact that the dose of cisplatin (30 mg/m^2/week) was lower than the dose used in a previously published phase III study in Hong Kong (40 mg/m^2/week).[71] This could be partly due to the better rate of compliance to chemotherapy where 78% of patients had six cycles of chemotherapy, compared to 44% in the Hong Kong study.[71,87] The 5-year OS rate of 85.8% is within the range reported by the Hong Kong NPC study group for stage II to III NPC.[1] However, because 2DRT was used in this study, the applicability of this study's data on current practice should be interpreted with caution in light of the now broader application of IMRT. Further studies on how patients with stage II NPC should be selected for concurrent chemoradiotherapy using plasma EBV DNA level are warranted.[111]

Prognostication with Plasma Epstein-Barr Virus in Patients Undergoing Cytotoxic Therapy

The almost universal presence of EBV genome in nonkeratinizing NPC tumors has opened up the opportunity of developing a new tumor marker, based on the detection of EBV DNA fragments in patient's blood. There is now ample evidence to show that plasma level of EBV DNA reflects tumor burden and disease stage in patients with EBV-positive NPC, and this level can be quantified accurately and reliably using a quantitative real-time PCR (qRT-PCR) technique that targets two regions of the EBV genome—the BamHI-W and EBNA-1 regions.[112–117] The reproducibility and relative affordability of this biomarker has enabled its validation in large-scale multicenter prospective studies and broadened its utility in the therapeutic monitoring of patients undergoing cytotoxic therapies. Kinetic studies in NPC patients undergoing radical RT have shown that the median half-life of

plasma EBV DNA is around 3.8 days,[115] and the prognostic role of plasma EBV DNA has been investigated in patients with locoregionally advanced NPC undergoing radical RT. In a study at the Prince of Wales Hospital (Hong Kong), patients with plasma EBV DNA levels of over 500 copies per mL at 6 to 8 weeks following RT were found to have a relative risk of cancer recurrence of 11.9 (95% CI 5.53 to 25.43).[118] This plasma cutoff has a positive and negative predictive value for NPC recurrence of 87% and 83%, respectively. A subsequent study also found that detection of an elevated plasma EBV DNA level at an earlier time-point during RT has been similarly associated with a higher risk of recurrence, with an HR for distant failure of 12.02 (95% CI 2.78 to 51.93).[119] This suggests that plasma EBV DNA monitoring during and after RT may be useful in identifying those patients who may benefit from more intensive systemic therapy. For patients undergoing palliative chemotherapy for metastatic NPC, plasma EBV DNA half-life analyzed during the first 4 to 5 weeks of therapy may predict radiologic tumor response and survival.[120]

To test the hypothesis that patients with elevated plasma EBV DNA at 6 to 8 weeks after RT may benefit from having adjuvant chemotherapy compared with observation alone, the Hong Kong NPC Study Group is conducting a multicenter phase III study (NPC0502) where patients with detectable plasma EBV DNA level will be randomized to adjuvant cisplatin and gemcitabine for six cycles or observation alone. To date, over 500 patients have been recruited with 95 patients having detectable EBV DNA who were subsequently randomized (NCT00370890). In an effort to standardize plasma EBV DNA assay across different centers as a prelude to conducting multicenter, multinational clinical trials where plasma EBV DNA will be used as an integral biomarker, four major centers from the United States, China, Hong Kong, and Taiwan have reported the first international collaborative exercise in the harmonization of quantitative RT–PCR analysis of plasma EBV DNA.[121] An international study led by the NRG has been initiated in which patients with persistently positive plasma EBV DNA following chemoradiotherapy will be randomized to either adjuvant cisplatin–5FU or gemcitabine–paclitaxel, whereas patients with negative plasma EBV DNA following chemoradiotherapy will be randomized to either cisplatin–5FU or observation. The NPC0502 and NRG HN001 studies are critical in addressing the question of how patients can be optimally selected for

therapeutic intensification soon after completion of definitive RT.

Treatment of Recurrent Nasopharyngeal Carcinoma

Treatment of Locoregional Recurrence

Locoregional control in NPC has improved in the last two decades[4]; however, 10% of all patients (20% to 25% in the T4 subgroup) still suffer from local failure despite modern treatment.[4,28,122] Latency for local recurrence varies widely, but the peak incidence is usually observed between the 2nd and 3rd year after primary RT, whereas late recurrence occurring beyond the 5th year is relatively uncommon.[123,124] Because the majority of patients with local recurrence do not have synchronous distant relapse,[124,125] aggressive salvage approach has been advocated because long-term survival is possible. Treatment options include surgery or reirradiation with curative intent, whereas palliative chemotherapy may be considered for those patients who are unfit for aggressive treatment. Unfortunately, therapeutic margin is narrow especially for those patients with advanced local recurrence. Careful patient selection is important in maximizing the therapeutic ratio, and therapeutic decisions should generally be based upon important factors such as the stage at recurrence, tumor volume, latency from primary treatment, pre-existing late complications, and general well-being of the patients. In a retrospective review of 275 NPC patients with local recurrence from Hong Kong, the 3-year OS rate for the entire cohort was 74%.[125] Patients who received salvage treatment had a significantly better OS than those who did not, but a subgroup analysis failed to find any survival advantage in patients with stages rT3 to rT4 disease. There was also no significant difference in survival between patients treated with radical RT or surgery.[125] There is a lack of randomized study comparing surgery versus reirradiation in patients with very early rT stage disease or comparing more aggressive treatment versus conservative approach in more advanced local recurrence. The current treatment recommendation is merely based on retrospective data and may change with time as therapeutic technologies evolve.

The efficacies of brachytherapy, high-dose external reirradiation or surgery are comparable in terms of treatment outcome in patients with early local recurrence, but their toxicity profiles are quite different. Brachytherapy is only suitable for small recurrences confined to the central nasopharynx (rT1) because the anchorage of radioactive source at the lateral wall or outside the nasopharynx would be technically difficult. External beam reirradiation is an alternative to surgery for rT2 disease, and it is often the only option for more advanced disease (advanced rT2, rT3-4) in which surgical resection is not feasible. Nasopharyngectomy is mainly reserved for tumors that do not involve the skull base or internal carotid artery (ICA) (rT1 and limited rT2). Depending on the location and extent of tumor involvement, different surgical approaches have been employed.[126–140] From these studies, the 5-year local failure-free rate for rT1 lesions after surgery has been reported to be ~65% to 77% and the corresponding disease-free survival rate ~54% to 73%. For regional recurrence, radical neck dissection is the standard treatment because the outcome of surgery is significantly better than reirradiation.[141–144] Interestingly, more aggressive surgical approaches that involved vascular bypass and cranial–facial resection have been tried in more advanced tumors, and their long-term results are eagerly awaited.

Reirradiation

Understanding the radiobiology of reirradiation is important to achieving the best clinical result. Whereas high reirradiation dose (60 Gy) is essential for tumor control, it will also increase the risk of mortality if the normal tissue tolerance is exceeded. Lee et al.[121] showed that the hazard of local failure was decreased by 1.7% per Gy of reirradiation given, whereas the hazard of toxicity was increased by 4.2% per Gy of primary RT. Partial recovery of normal tissues, including the brain and spinal cord, was observed as early as 6 to 12 months after the primary course.[121] Historically in patients who were reirradiated for local recurrence, long-term survival can be expected if a sufficient amount of radiation dose in excess of 60 Gy could be given.[121,145–149] Tolerance of normal tissue to cumulative radiation is the main dose-limiting factor, particularly in the brain and spinal cord. Thus, the fundamental principle of reirradiation should be aimed at concentrating high radiation dose to the tumor target with a rapid dose gradient to maximize the protection of adjacent normal organs. Brachytherapy, stereotactic

radiosurgery (SRS), or external beam reirradiation have been evaluated in several studies (Table 11.8).[121,146–148,150–165] As a general working rule for reirradiation, brachytherapy is applicable only for rT1 tumors, whereas SRS or fractionated stereotactic radiotherapy (FSRT) (with or without intensity modulation) is applicable for rT1 or T2 tumors. For more extensive T3 and T4 recurrences, IMRT and fractionated stereotactic IMRT (FS-IMRT) with or without chemotherapy and with or without dose escalation using brachytherapy or SRT are all regarded as reasonable options in contemporary practice.

Table 11.8 Results from Series Using Radiotherapy for NPC Local Recurrence

Author	Patient *N* (rT1%)	Radiation Method and Median Dose	FU Year (Median)	Local Control (%)	Overall Survival (%)
Lee et al.[121]	654 (35% rT1)	2DRT (40–46 Gy) + brachytherapy	5	23	16
Chang et al.[148]	186 (23% rT1)	2DRT (50 Gy) +/– SRS (8–15 Gy)	3	–	22
Teo et al.[150]	103 (22% rT1)	2DRT (66 Gy) +/– brachytherapy	5	15	8
Chua et al.[151]	97 (34% rT1)	2DRT (60 Gy) +/– brachytherapy	5	–	36
Leung et al.[147]	91 (41% rT1)	2DRT (50 Gy) +/– brachytherapy	3	38	30
Pryzant et al.[152]	52 (51% rT1)	2DRT (57 Gy) +/– brachytherapy	5	35	21
Oksuz et al.[153]	41 (22% rT1)	2DRT (50 Gy)	5	23	28
Zheng et al.[154]	86 (18% rT1)	3DRT (68 Gy)	5	71	40
Chua et al.[155]	24 (58% rT1)	SRS (12.5 Gy/1 Fr)	3	30	52
Low et al.[156]	31 (all rT1)	SRS (18 Gy) + brachytherapy	5	57	53
Wu et al.[157]	56 (68% rT1-2)	FSRT (48 Gy/6 Fr)	3	75	46 (DSS)
Seo et al.[158]	35 (43% rT1)	FSRT (33 Gy/3–5 Fr)	5	79	60
Leung et al.[146]	30 (47% rT1)	FSRT (54 Gy/18 Fr)	5	57	40
Ozyigit e al.[159]	24 (21% rT1)	FSRT (30 Gy/5 Fr)	2	82	64 (DSS)
	27 (15% rT1)	3DRT (57 Gy) +/– brachytherapy	2	80	47 (DSS)
Koutcher et al.[160]	13 (69% rT1)	3DRT (45 Gy) + brachytherapy (20 Gy)	5	53	57
	16 (25% rT1)	IMRT (83%) (59.4 Gy)	5	52	60
Lu et al.[161]	49 (8% rT1)	IMRT (71.4 Gy)	1	100% (9 mo)	–
Han et al.[162]	239 (7% rT1)	IMRT (69.94 Gy)	5	86	45
Chua et al.[163]	31 (10% rT1)	IMRT (56.8 Gy) +/– SRS (8.5–12.5 Gy)	1	61	63
Chen et al.[164]	54 (6% rT1)	IMRT (68.5 Gy)	2	66	44
Qiu et al.[165]	70 (4% rT1)	IMRT (70 Gy)	3	50	52

2D/3D, two/three dimensional; RT, radiotherapy; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic RT; IMRT, intensity-modulated RT; DSS, disease-specific survival.

Brachytherapy

Brachytherapy can deliver a high dose to a small tumor volume and is applicable to tumors confined to the nasopharyngeal cavity and away from the skull base. Intracavitary brachytherapy is a more common approach nowadays. It has been used most often as a boost after nasopharyngectomy or external beam reirradiation. Combined external and intracavitary approach was shown to be less toxic than external reirradiation alone in some retrospective series, most of which employed 2DRT.[121,147,151,152,160] The advantage of brachytherapy boost exists even when more conformal external RT technique is used at the outset. Koutcher et al.[160] showed that combined conformal RT/IMRT (45 Gy) and brachytherapy (20 Gy) incurred significantly less severe late toxicity than conformal RT/IMRT alone (59 Gy) (8% vs. 75%) for the same degree of tumor control and OS.

Stereotactic Radiosurgery/Fractionated Stereotactic Radiotherapy

SRS was initially applied to the treatment of small volume T1/2 recurrence because of its high degree of precision and steep dose gradient.[155,156,166–168] For tumor that is large, irregular, or close to the brain or major vessels, hypofractionated SRT is radiobiologically less damaging to the normal tissue. A joint analysis on 56 patients with early local recurrence showed 75% local control rate at 3 years using 48 Gy in 6 fractions.[157] Chua et al.[167] compared SRS (median 12.5 Gy single dose) with hypofractionated SRT (median 35 Gy in 4 to 6 fractions) in a matched cohort analysis consisting of 86 rT1-4 patients. FSRT was associated with a significantly higher 3-year local control rate than SRS (83% vs. 51%) especially in the rT2 to T4 subgroup, but the OS was similar and the incidence of severe late complications was higher in the SRS group.[167] Seo et al.[158] used CyberKnife SRT to deliver a median dose of 33 Gy in 3 to 5 fractions to 35 patients (43% rT1) and achieved 5-year local control of 79% and OS of 60% without serious neurologic complication. In a retrospective comparison of CyberKnife FSRT (30 Gy in 5 fractions) versus 3DCRT (median dose of 57 Gy), Ozyigit et al.[159] observed similar 2-year local control between the two groups (82% vs. 80%), but FSRT had significantly lower incidence of grade 3 or more overall rate of late toxicities (21% vs. 48%). However, the incidence of massive hemorrhage was substantially higher in the FSRT group (17% vs. 4%), whereas the treatment mortality rate remained high in both groups (13% vs. 15%).[159]

These studies suggest that a high dose is needed for a successful tumor control, which comes at a price of increased severe morbidities or even mortality particularly in patients with more advanced recurrence. Along with the restriction of dose and volume of neurovascular tissue irradiation, other factors such as dose homogeneity, dose falloff, and the use of lower dose per fraction are all important dosimetric factors that can affect the outcome of treatment. Advances in frameless SRT in conjunction with image-guidance technologies enhance the feasibility for more protracted fractionation, which may hopefully help to reduce the risk of neurovascular damage associated with SRS and hypofractionated SRT.

Intensity-modulated Radiotherapy

IMRT can potentially improve the therapeutic ratio by achieving a more optimal dose distribution between tumor target and critical normal organs, and IMRT has therefore been evaluated in the treatment of NPC local recurrence. Han[162] and Lu et al.[161] reviewed 239 patients (46% rT4) who received IMRT for local recurrence. The 5-year OS was 44.9% and local recurrence-free survival was 85.8%, but as much as 34.7% of patients died of radiation injury. Qiu et al.[165] reported the outcome of 70 patients retreated with IMRT at a median dose of 70 Gy and reported a 2-year locoregional recurrence-free survival and OS of 65.8% and 67.4%, respectively. Moderate to severe late toxicities were noted in 35.7% of patients (17% deafness and 24% cranial neuropathy).[165] In a recent report by Chen et al.[164] using 68.5 Gy IMRT to treat 54 patients with rT1 to rT4 recurrences, the 2-year local PFS was 64% and OS of 44%. Severe late toxicity was seen in 48% of patients (including 11% massive bleeding, 18.5% temporal lobe necrosis, 20% dysphagia, and 31.5% mucosal ulceration), and the treatment-related death occurred in 25% of patients.[164] The high incidence of radiation damage is still the major limitation for the successful delivery of high-dose radiation to the recurrent tumor, despite the use of IMRT and stereotactic setup. The treatment outcome for rT4 disease is particularly disappointing. Careful selection of patients with favorable prognostic factors will help to avoid futile treatment and undesirable complications. Using prognostic factors such as tumor volume, rT stage, rN stage, preexisting toxicity, age, and performance status to calculate a prognostic score, patients within the “high-risk” category have a 5-year survival of 8% only despite the use of IMRT. This group of high-risk patients should better be managed conservatively.[169]

Salvage Surgery

For local recurrence, different surgical approaches have resulted in different outcome and complication depending on the location and extent of tumor involvement. Overall, the 5-year local failure-free rate for rT1 lesions after surgery was 65% to 77%, and the corresponding disease-free survival rate was 54% to 73%.[126–140] The surgical outcome is worse with more advanced lesions because it is difficult to achieve adequate surgical margin without damaging critical neurovascular structures such as the carotid artery or cranial nerves.

Advances in minimally invasive surgery have enabled small tumors located in the posterior wall of the nasopharynx to be resected via endoscopic approach through the nasal or oral cavity.[140,170–172] En bloc resection is performed with an electric knife or a laser. Microwave coagulation therapy has also been used successfully through transnasal route.[173] Resection of larger tumor with more lateral extension can now be performed with the versatile “endowrist” of the robotic instruments (transoral robotic surgery, TORS).[174] TORS is currently only limited to the resection of tumors not close to the ICA because the robotic arm lacks tactile surveillance for the carotid pulsation. For more bulky recurrent tumors, an open surgical approach is required for more adequate visual exposure. The nasopharynx can be accessed through the infratemporal fossa from the lateral approach,[175,176] with possible complications of conductive hearing loss and trigeminal nerve dysfunction. When the tumor is located in the central nasopharynx without lateral extension, resection can be performed from the inferior aspect via the transpalatal, the transmaxillary, or the transcervical approach.[177,178] Maxillary swing nasopharyngectomy is another widely practiced anterolateral approach that provides adequate exposure of the tumor in the nasopharynx and the parapharyngeal region. Resection of tumor in conjunction with any parapharyngeal or even retropharyngeal disease is feasible with this approach.[179] In an update on 312 patients using the maxillary swing approach, Chan et al.[180] reported a 5-year actuarial local control rate of 74% and OS of 62%. A number of prognostic factors such as tumor size, resection margin status, and the presence of gross tumor in the sphenoid sinus were found to influence local tumor control. The resection margin status, synchronous cervical nodal recurrence, and cavernous sinus

invasion were found to negatively affect OS after this surgical approach.[128] The same group also evaluated staged operations (intracranial–extracranial vascular bypass, craniofacial resection, and microvascular free flaps) on advanced recurrences that were initially deemed to be inoperable due to ICA encasement or skull base invasion. With this extended approach, 81.8% of curative resection rate was achieved on 22 patients, and the OS was 100% at a mean follow-up of 38.8 months.[181] Common surgical complications include facial numbness, ectropion, epiphora, trismus, palatal fistula, and middle ear effusion.

For patients with regional nodal recurrence, radical neck dissection is the standard treatment because the outcome of surgery is significantly better than reirradiation.[143,144] Chua et al.[144] analyzed 43 patients with synchronous locoregional relapse and found that the 3-year nodal control rate after radical neck dissection was 65%, compared with 24% by reirradiation alone. Previous irradiation also limits the amount of radiation that can be given at recurrence without significant toxicities to vital structures like the brachial plexus, carotid artery, and spinal cord. In contrast, the outcome of patients after radical neck dissection has made steady progress as a result of better imaging support and surgical technique, achieving a 5-year regional control rate and OS rate of 68% and 58% to 66%, respectively.[141,142] Modified radical neck dissection has been advocated in some institutions with the aim of preserving the patient's quality of life by sparing the internal jugular vein or spinal accessory nerve. However, this should be regarded as investigational at present because the tendency of isolated tumor cell clustering, muscle invasion, and extranodal extension from these recurrent nodal diseases may jeopardize the rate of complete resection.

Treatment of Metastatic Disease

The majority of cases of metastatic NPC diagnosed in endemic regions are due to distant failures following definitive RT, although very few patients present with distant metastases from the outset.[21,182] In the study by Hong Kong NPC Study Group, distant metastasis was the most common cause of treatment failure with a 5-year actuarial rate of 14.9% for all disease stages.[183] Of the 476 patients who developed distant metastasis, 79.6% presented with distant metastasis alone, 12.3% with locoregional recurrence initially followed by distant metastasis, and 8.1% presented with distant and

locoregional recurrence synchronously.[183] Patients who develop locoregional recurrence were also at higher risk of developing subsequent distant metastases at a rate of 20% to 34%.[183] The most common site of distant metastasis was the bony skeleton followed by the liver and lung.[184–186] The prognosis of patients with metastatic NPC is quite variable with a marked heterogeneity of OS observed among different metastatic sites, and patients with metastases limited to the lung have the longest survival with a median OS of 3.9 years.[183–185,187] Over 80% of distant recurrences tend to present within 3 years after definitive RT, but recurrences beyond 5 years are not uncommon.[182,188]

Long-term survival (beyond 5 years) has been well described in metastatic NPC,[23,182,189] and most long-term survivors tend to have younger age, male gender, and prior treatment with platinum-based chemotherapy.[23,182,187,189] Retrospective series suggest that patients with distant metastases that were amenable to multimodal treatment seemed to live longer than did those who received chemotherapy or local therapy alone.[23,187] This underscores the important role of multidisciplinary approach in the management of metastatic NPC.

Although chemotherapy has never been compared with supportive care alone in metastatic NPC, platinum-based chemotherapy is regarded as the therapeutic cornerstone because of their well-proven activity in the literature. Most of the data are derived from single-armed phase II studies conducted in a single center; thus, there is a paucity of randomized trials comparing different regimens. The results of these nonrandomized studies need to be interpreted with caution for several reasons. Some of these studies were underpowered and the enrolled subjects could be quite heterogeneous in terms of histology, disease burden, sites of metastases, and extent of prior exposure to adjunctive chemotherapy during RT. The inclusion of a higher proportion of patients with only locoregional recurrences may potentially underestimate the tumor shrinkage rate, as some irregularly shaped recurrent tumors such as those at the skull base or the nasal cavity may be hard to assess using the Response Evaluation Criteria in Solid Tumors (RECIST).[190,191]

First-line Clinical Trials

In the late 1970s, nonplatinum agents such as cyclophosphamide, doxorubicin, bleomycin, and methotrexate were reported to yield single-agent response rates of 38%, 39%, 28%, and 17%, respectively, in patients with recurrent NPC.[192] Since the introduction of cisplatin in the treatment of squamous head and neck cancers in the early 1980s, the earliest reports on the use of platinum-based chemotherapy in NPC described response rates of over 50% in patients with recurrent NPCs who were treated with cisplatin and 5-fluorouracil (5FU) or with cisplatin–bleomycin–vincristine as a triplet or other combinations with more than three drugs including bleomycin, vincristine, methotrexate, and/or doxorubicin.[193,194] Several prospective phase II studies conducted in predominantly chemotherapy-naïve patients with recurrent or metastatic NPC have been published (Table 11.9).[193–208] The majority of these studies reported impressive and durable response rates with multiple drug combinations of three or more drugs (maximum of five drugs). However, the incidence rates of grade 3 to 4 marrow toxicities were high with occasional reports of treatment-related deaths.[199,201,209]

Table 11.9 Selected Phase II Trials of Chemotherapy in First-Line Treatment of Metastatic or Recurrent Nasopharyngeal Carcinoma

First Author	Year	Sample Size	Regimen	Overall Response (%)	Median TTP/ PFS (m)	Median OS (m)
Decker[193]	1983	12[a]	Cisplatin–5FU Cisplatin–bleomycin–vincristine	67 67	–	– –
Al-Kourainy[194]	1988	17[a]	Cisplatin–5FU Cisplatin + bleomycin + vincristine +/– methotrexate +/– doxorubicin	53	–	–
Boussen[195]	1991	49	Cisplatin–bleomycin–5FU	78	–	NR
Wang[196]	1991	25	Cisplatin–5FU	76	–	–
Au[197]	1994	24	Cisplatin–5FU	66	8	11
Chi[198]	1994	35[b]	Cisplatin–5FU–leucovorin	100	–	–
Siu[199]	1998	90	CAPABLE	80	–	14
Tan[200]	1999	32	Carboplatin–paclitaxel	75	7	12
Taamma[201]	1999	26	Cisplatin–5FU–bleomycin–epirubicin	78	–	–
Ngan[202]	2002	44	Cisplatin–gemcitabine	73	10.6	15
Chua[203]	2005	19	Cisplatin–docetaxel	56	7.3	12.4
Leong[204]	2005	32	Carboplatin–paclitaxel–gemcitabine	78	8	18.6
Ma[205]	2009	42	GEMOX	56	9	19.6
Li[206]	2008	48	Cisplatin–capecitabine	62.5	7.7	13.3
Chua[207]	2012	44	Cisplatin–capecitabine	53.8	7.3	28
Ji[208]	2012	47	Cisplatin-weekly docetaxel	70.2	9.6	28.5

[a]Heterogeneous population including squamous and nonsquamous histologic subtypes.

[b]These studies enrolled a few previously treated patients.

[c]Only 44 patients treated with chemotherapy without radiotherapy were outlined here.

NR, not reached; 5FU, 5-fluorouracil; GEMOX, gemcitabine and oxaliplatin; TTP, time to progression; PFS, progression-free survival; OS, overall survival.

With the introduction of more modern regimens in the late 1990s, platinum-based doublets using taxanes, gemcitabine, and capecitabine have gained increasing popularity in contemporary practice because of their efficacy, safety, and convenience. As shown in Table 11.9, regimens such as cisplatin–gemcitabine, carboplatin–paclitaxel, and cisplatin–capecitabine could yield response rates that are comparable to the older regimens with fewer grade 3 to 4 hematologic toxicities.[200,202,206,207,210] Ngan et al.[202] showed that patients with distant metastasis alone had a higher response rate (80%) than those with locoregional disease (55%) to cisplatin–gemcitabine. This finding highlights the importance of taking into account of the proportion of enrolled subjects with distant versus locoregional disease when interpreting response rates from single-armed phase II studies in NPC.[202] The clinical experience with docetaxel in NPC has been marred by two reports of excessive myelotoxicities,[203,211] but recently published Korean study found that an alternative schedule of cisplatin and weekly docetaxel was very well tolerated in patients with NPC.[208] This result is promising and may re-establish the role of docetaxel in the palliative treatment of NPC.

Various platinum derivatives such as the second-generation agents carboplatin and nedaplatin and the third-generation agent oxaliplatin have been evaluated in NPC. Nedaplatin is a cisplatin analogue that has been evaluated as a substitute for concurrent cisplatin during RT and in patients who had failed prior cisplatin in the palliative setting.[212,213] Oxaliplatin has been investigated in combination with gemcitabine in the "GEMOX" regimen, with a median OS (19.6 months) and time to progression (9 months) that were comparable to the report on cisplatin–gemcitabine.[202,205] These data suggest that oxaliplatin could be an effective substitute for cisplatin in patients who are intolerant to cisplatin. Although there is no randomized data to suggest which platinum is the drug of choice in the palliative setting, cisplatin and carboplatin are often regarded as the prevailing backbone for

first-line chemotherapeutic regimens for recurrent or metastatic NPC. Overall, for patients with good performance status and predominantly distant metastases, the use of platinum-doublets should be expected to yield at least a response rate between 56% and 70% and a median TTP between 6 and 10 months. The OS rates of patients enrolled in phase II studies have improved over the last decade, and this may be partly due to improvement in supportive care, less toxic chemotherapeutic agents, and the increasing awareness that certain patients subgroups with only pulmonary metastases may benefit from a more aggressive and multimodal therapeutic approach.

Clinical Trials of Chemotherapy in Subsequent Lines

For patients who fail prior platinum-based chemotherapy for recurrent NPC, there is no universally accepted standard of care in terms of drug regimen Table 11.10.[213]–[223] outlines some of the published phase II studies on patients who have failed one or more lines of prior chemotherapy. In the studies of single agents, the reported response rates varied between 14% and 48% and the median OS rates between 7 and 16 months. The durability of treatment response varies considerably across these studies, with median time to progression ranging from 1.5 to 7.5 months. Most of the studies described in Table 11.10 involved nonplatinum agents, and the sample sizes of these studies are too small to draw any conclusions about the merits of using multiagent regimens over single agents in patients who progressed after first-line platinum-based therapy. It is also difficult to estimate the magnitude of benefit of chemotherapy in this setting, as chemotherapy has not been compared with supportive care alone. These views are reflected in some guidelines from the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO), although significant differences in institutional preferences exist.[224,225]

Table 11.10 Selected Phase II Trials of Chemotherapy in Subsequent Lines of Treatment in Metastatic or Recurrent Nasopharyngeal Carcinoma

First Author	Year	Sample Size	Regimen	Overall Response (%)	Median TTP (mo)	Median OS (mo)
Chua[214]	2000	19	Ifosfamide, 5FU, leucovorin	56	6.5	NR
Airoldi[215]	2002	12	Carboplatin–paclitaxel	25	–	9.5
Foo[216]	2002	27	Gemcitabine	48	5.1	7.2
Chua[217]	2004	17	Capecitabine	23.5	4.9	7.6
Poon[218]	2005	28	Irinotecan	14	–	11.4
Wang[219]	2006	39	Gemcitabine–vinorelbine	36	–	11.9
Zhang[220]	2008	32	Gemcitabine	43.5	5.1	16
Ngeow[221]	2011	30	Docetaxel (weekly)	37	5.3	12.8
Zhang[222]	2012	35	Pemetrexed	2.9	1.5	13.3
Yau[223]	2012	15	Cisplatin–pemetrexed	20	7.5	NR
Peng[213]	2013	48	Nedaplatin–capecitabine	41.7	5.8	12.4

mo, months; TTP, time to progression; OS, overall survival; NR, not reported.

Novel Therapy

Targeted Therapy

To date, the clinical evaluation of molecularly targeted therapies in NPC has mainly involved inhibitors against the epidermal growth factor receptor (EGFR) and its related signaling kinases, and antiangiogenic agents against vascular endothelial growth factor receptor (VEGFR)-mediated signaling. Most of the published reports have mainly been single-arm phase II studies enrolling unselected populations of patients with recurrent or metastatic NPC who have been heavily pretreated with chemotherapy. A few studies have investigated the feasibility of combining antibodies with concurrent chemoradiotherapy in locoregionally advanced NPC.

Epidermal Growth Factor Receptor Inhibitors

One of the earliest categories of targeted agents that have been evaluated in NPC was the EGFR inhibitors. The *EGFR* gene is among one of several important oncogenes such as *RAS*, *C-MYC*, *C-MET*, and *BCL-2* that are frequently up-regulated in NPC.[226] *EGFR* gene amplification and overexpression can be found in 40% and 80% of NPC tissues, respectively.[227,228] In phase II trials of patients with recurrent or metastatic NPC, the lack of activity of gefitinib as monotherapy may be attributed to the lack of activating EGFR mutations in NPC.[229–231] The combination of

cetuximab and carboplatin have shown modest activity in this patient population in a multicenter phase II study, with a partial response rate of 11.7% and stable disease rate of 48.3%.[232] However, the response was short-lived as the time to progression was just 2.7 months for the whole group.

Antiangiogenesis Inhibitors

The class of agents that has currently reached the most mature stage of clinical development in NPC is the inhibitors of angiogenesis. Sunitinib and pazopanib are the predominantly anti-VEGFR, multitargeted kinase inhibitors that have been evaluated in phase II studies in heavily pretreated patients with recurrent or metastatic NPC.[233–236] In the studies on sunitinib and pazopanib, the majority of patients experienced prolonged SD, and objective responses were uncommon (<6%). However, the pazopanib study failed to reach its predefined level of drug response, whereas the study of sunitinib was prematurely terminated because of excessive bleeding–related toxicities.[233,236] The risk of serious bleeding from sunitinib seemed to occur in patients with previously irradiated locally recurrent tumor involving the ICA.[233] The authors recommended that such patients should be excluded from future studies of antiangiogenic agents. The activity of the anti-VEGF antibody bevacizumab is currently being evaluated in a phase III study comparing chemotherapy alone versus chemotherapy and bevacizumab in the first-line treatment of recurrent and metastatic NPC in China.

Incorporation of Targeted Therapy with Radiotherapy

For patients with nonmetastatic stage III to IV NPC, ~20% of patients with T3 to T4 NPC still develop locoregional recurrence despite the use of modern RT techniques.[183] One novel strategies that may enhance local control is the incorporation of novel radiosensitizers such as antibodies against EGFR or VEGF. At the Prince of Wales Hospital in Hong Kong, the safety of adding weekly cetuximab to concurrent cisplatin at a weekly schedule and IMRT was investigated in patients with nonmetastatic stage III to IV NPC.[237] Although the 2-year PFS rate of 86.5% (95% CI, 74.3% to 98.8%) compared favorably with historic data (2-year PFS of 76%),[71] the rate of acute mucosal toxicities encountered in this study (grade 3 to 4 oropharyngeal mucositis of 87%) were much higher than the rates reported with 2DRT and IMRT—

where the grade 3 to 4 mucositis was around 40% to 48%.[46,71] In the RTOG 0615 study, bevacizumab was evaluated in combination with concurrent cisplatin at a 3-weekly schedule and IMRT in patients with stage IIb to IVb NPC.[238] The primary endpoint was the incidence of grade 3 to 4 bleeding or any grade 5 events. The result showed that bleeding episodes were mostly grade 1 to 2 in severity and there were no treatment-related deaths. Although cross-trial comparison is fraught with bias, the 2-year PFS rate of 74.7% (95% CI 61.8% to 87.6%) appears to be similar to historic data with chemoradiotherapy alone in a phase III study as mentioned above.[71]

Immunotherapy

EBV is ubiquitous in nonkeratinizing NPC, and EBV antigens have been exploited as potential targets for immunotherapy. However, NPC only expresses a set of poorly immunogenic latency type II viral antigens, namely, EB nuclear antigen (EBNA)-1 and latent membrane protein (LMP) 1 and LMP2. EBNA-1 is expressed frequently in NPC and is a dominant target for CD4 T cells. LMP1 and LMP2 are expressed in around 50% of NPC tumors and are both targets for CD8 cytotoxic T lymphocytes (CTL). Although LMP1 is the key EBV oncogenic protein, it is poorly immunogenic, and thus, LMP2 is a more likely target antigen for a CD8 CTL-based therapy.[239,240] Studies in healthy subjects revealed that these latent proteins are not the dominant targets of T-cell response associated with natural EBV infections. However, some of the latent proteins such as EBNA-3, LMP2, and, less commonly, EBNA-2, EBNA-LP, and LMP1 can provide immunodominant epitopes that are restricted through the HLA-1 and HLA-A2 family of alleles.[241] The objective of boosting anti-EBV responses in circulating CD8 T cells in NPC patients, such as boosting CD8 immunity to LMP2 epitopes, has formed the basis for the clinical development of vaccine and adoptive T-cell therapies in NPC.

The use of autologous EBV-specific CTL in the treatment of patients with advanced NPC has been shown to be safe and effective in inducing LMP2-specific immune responses, and sustained clinical responses have been reported in several clinical trials.[242–245] Adoptive T-cell transfer is an ideal form of personalized therapy that has the potential to enhance long-lasting antitumor immunity, but the process of T-cell expansion is costly, labor intensive, and restricted to specialist centers. An alternative way of T-cell

expansion that could circumvent some of these limitations is a vaccine-based approach as reported by Smith et al.,[246] on an adenovirus vector–based polysaccharide vaccine, which contained the combined antigenic epitopes of EBNA-1, LMP1, and LMP2. The feasibility of a sequential approach of upfront carboplatin–gemcitabine followed by LMP1- and LMP2-specific CTLs in the first-line treatment of recurrent and metastatic NPC has also been recently reported.[247] The median OS almost reached 30 months (95% CI: 20.8 to 39.3 months), which compared favorably with historic data on survival for patients who received first-line chemotherapy alone (Table 11.9). Interestingly, atypical responses were observed in some patients, where there was an initial radiologic tumor progression, followed by late responses.[247]

Two main vaccine-based approaches have been reported to date, namely, autologous dendritic cell-based vaccines and a non–cell-based approach of using a modified vaccinia Ankara (MVA) recombinant vector that expresses tumor-associated viral antigens. Lin et al.[248] demonstrated the feasibility of a vaccine containing dendritic cells that were pulsed with LMP2-derived peptides, in boosting peptide-specific T-cell responses and durable tumor response in a small group of patients with advanced NPC. Another dendritic cell-based method was an adenovirus–DeltaLMP1–LMP2 transduced dendritic cell vaccine, but the investigators did not observe any LMP1- or LMP2-specific T-cell response in patients with metastatic NPC.[249] Using a total different approach, Hui et al.[250] investigated an MVA-based vaccine, which was constructed using sequences cloned from a typical Chinese EBV strain and encodes a functionally inactive fusion protein containing the CD4 epitope–rich C-terminal half of EBNA-1 and the CD8 epitope–rich LMP2A. The combination of both EBV antigens has the potential advantage of boosting host response to both CD4- and CD8-mediated immunity. A phase I study has demonstrated the safety and immunogenicity of this vaccine in patients with NPC following definitive RT. T-cell responses to one or both vaccine antigens were increased in most patients in a dose–response manner. This vaccine is currently being evaluated in a phase II trial in patients who have either residual plasma EBV DNA following RT or residual disease following response to palliative chemotherapy for metastatic NPC (NCT01094405).

Conclusion

Advances in the prognostication and treatment of NPC have significantly contributed to an improvement in patient survival in endemic regions such as Hong Kong. RT remains the cornerstone in the treatment of early disease, and a multidisciplinary approach to the multimodal treatment of advanced and recurrent disease has largely become the standard of care in many expert centers. As more long-term data on safety and efficacy are now available, IMRT has been widely adopted in routine practice. Controversy remains in the role of concurrent chemotherapy in stage II NPC and the optimal application of plasma EBV DNA in selecting patients for adjuvant chemotherapy following definitive chemoradiotherapy. The systemic treatment of recurrent and metastatic NPC is challenging, and immunotherapy using vaccine-based approaches is an area of active research at present.

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12 Cancer of the Lip

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Approximately 25% of all carcinomas of the oral cavity involve the lips, making the lips the most commonly affected subsite in the oral cavity. The prominent location of cancers of the lip allows for early detection of pathology. The lips play such a prominent role in how we present ourselves to the outside world that any abnormality is immediately noticed and reacted to. The fact that lesions of the lips are detected so early makes treatment relatively easy and successful, making cancer of the lip one of the most curable cancers of the head and neck. Unfortunately, even with the prominent location and ease of detection, as many as 15% of the cases, the disease will demonstrate aggressive behavior manifested by recurrence, metastasis, and death from disease. Late presentation due to neglect or poor access to health care accounts for a portion of these cases. The vast majority of cancers of the lip are treated with local resection followed by repair through local tissue rearrangement. Reconstruction of larger defects after resection of larger tumors may require complex composite flaps to optimize both function and cosmesis.

ANATOMY OF THE LIP

The upper and lower lips are the most dominant feature of the lower third of the face. The area of the lips extends vertically from the subnasale to the mental crease and horizontally to each oral commissure. Embryologically, the lips are formed by the union of five facial processes. The upper lip is formed from the two lateral maxillary processes that fuse centrally with the frontomedian process, whereas two mandibular processes meet in the midline to form the lower lip.

The lip is a complex anatomical structure, which includes a muscular

layer that is a part of the oral sphincter, lying between a mucosal layer and the overlying skin. This muscular layer is composed of the orbicularis oris muscle, which is derived from the second branchial arch. The muscle fills most of the body of the lip and completely encircles the mouth creating the oral sphincter. This skeletal muscle helps in the regulation of food entrance and maintenance within the oral cavity. The orbicularis muscle of the lip is not a simple sphincter because, in its periphery, it receives fibers from the many different surrounding facial muscles. These act together with the orbicularis to produce the various shapes and functions that are possible with the lips, such as smiling, frowning, kissing, blowing, whistling, articulating speech, and closing the lips.

The most characteristic feature of the lip is the vermilion—a transitional mucosal surface that covers the free margin of the lip and bridges the external skin with the internal mucosa. The mucocutaneous junction forms the anterior vermilion border, whereas the posterior point of contact of the lips, when they are held closed, marks the posterior vermilion border.

Sensory innervation of the lip is supplied by the second and third division of the trigeminal nerve. The upper lip is supplied by the infraorbital branch of the maxillary nerve (V2), exiting from the infraorbital foramen. The oral commissure is supplied by the buccal branch of the mandibular nerve (V3). Lower lip sensation is supplied by the mental branch of the mandibular nerve, which enters the mandible as the inferior alveolar nerve at the inferior alveolar foramen. The nerve traverses the mandible and exits through the mental foramen as the mental nerve. The nerve transitions from posterior to the mandible to anterior as it passes through the mandible. As the nerve of the second branchial arch, the facial nerve provides lip motor innervation via the buccal and marginal mandibular branches. The buccal branch of the facial nerve supplies the upper lip, whereas the lower lip motor functions are supplied through the marginal mandibular branch.

The arterial supply to the lips is provided principally by the left and right facial arteries, from which arise first the inferior and then the superior labial arteries. These vessels encircle the left and right side of the mouth passing between the respective orbicularis and submucosa. Venous drainage is supplied by the left and right anterior facial veins. These run posterior to the facial arteries with their corresponding branches. Interconnections are abundant, and the total lip complex can survive on the contralateral supply.

Lymphatic drainage of the upper lip and oral commissure is accomplished by an interconnecting network of delicate vascular structures found in both the submucosal and subcutaneous tissue planes. This network goes on to drain into five collecting trunks on either side, which in turn drain laterally to the preauricular, infraparotid, submandibular, and submental lymph nodes. Embryonically, the central frontonasal process separates the lateral maxillary processes. As such, there is no contralateral drainage from the upper lip. By contrast, the mandibular processes of the lower lip fuse at midline, allowing numerous crossing anastomoses to occur. Lymphatic drainage to the lower lip therefore occurs to the submental and submandibular nodes bilaterally.

EPIDEMIOLOGY OF CANCER OF THE LIP

The incidence of cancer of the lip varies significantly throughout the world. It is presumed that the variations are due to such factors as race, environment, and personal habits. Overall, cancer of the lip is most commonly observed in the white, male, smoker, over the age of 50, with fair complexion and blue eyes. Thus, it should not be surprising that the highest incidence of lip cancer is reported among the white populations of Canada and Australia. More than 50% of oral cancers in Australians are located on the lip. Lip cancer is rare in the nonwhite populations, as darkly pigmented populations have greater amounts of protective pigment within their vermilion.[1]

Although a number of identified factors are felt to be associated with the development of cancer of the lip, ultraviolet light exposure is by far the greatest contributing factor and is associated with 90% of cases of cancer of the lip. Because the lips are located on the face, they are subjected to greater exposure to ultraviolet light than most of the other areas of the body. Eighty-eight percent to ninety-eight percent of cancers of the lip are found in the vermillion of the lower lip.[2] It is believed that this is caused by outward projection of the lower lip together with a downward angulation that favors direct exposure of the vermilion to overhead sunlight.

On the lower lip, cancer is most frequently found on the exposed vermilion border, arising at the point midway between the oral commissure

and midline. Cancer arises in the commissure of the lip in fewer than 1% of all cases. This rate is roughly proportionate to the actual exposed surface area. Although the upper lip is also outwardly projected, its vermilion surface faces downward, away from direct sunlight. Malignancy arising in the upper lip vermilion constitutes only 2% to 7% of reported cases.[3] When they occur, they most frequently arise near the midline where exposure to direct sunlight may be greatest.

Much of the evidence that has implicated ultraviolet light exposure as etiologic in cancer of the lip is derived from associations that have been made in case series studies and epidemiologic surveys. These studies and surveys show that at least one-third of patients who develop cancer of the lip have outdoor occupations, presumably subjecting them to substantial ultraviolet light exposure. UV radiation is known to produce mutations in DNA. When the body fails to repair these mutations, cancer may form. Regardless of the patient's age, the damaging effects of excessive solar exposure can be expected to be found in patients who develop cancer of the lip. Typical findings include generalized atrophy of the vermilion, loss of elastic fibers, atrophy of adipose tissue, and glandular elements, as well as cellular changes such as hyperkeratosis and atypia. Advanced chronic solar injury to the lip often produces fading of the sharp color contrast normally seen at the mucocutaneous line. Areas of the vermilion that have sustained particularly severe solar injury may display areas of chronic scaling or crusting (actinic cheilitis) that are analogous to actinic keratoses found in sun-damaged skin. In general, patients with cancer of the lip will often be found to have other sun-induced malignancies or premalignant changes in the surrounding vermilion and facial skin.

Exposure to tobacco products has clearly been shown to increase the risk for malignancy particularly within the oral cavity. The relationship between tobacco use and the development of cancer of the lip is less clear. The data so far have been based primarily on information obtained from various case series that have identified a large proportion of patients with cancer of the lip that has regularly used tobacco products. Some case controlled studies, however, have failed to support a distinct relationship of tobacco use with cancer of the vermilion of the lip.[4]

Immunosuppressed populations show a markedly increased risk for development of malignancies. This is particularly true for the development of

squamous cell carcinoma (SCC) of exposed cutaneous surfaces. The increased risk of lip cancer among renal allograft patients on immunosuppressive therapies may be as great as 30-fold.[5] People receiving higher doses of immunosuppressant’s tend to develop more nonmelanoma skin cancers than those on lower doses. These patients are also at an increased risk for development of second primary cancers of the lip.

A variety of other factors have been reported to have some association with the development of cancer of the lip. These include thermal injury, mechanical irritants, trauma, use of alcohol, poor oral hygiene, chemical exposure, influence of various infectious diseases, and prolonged exposure to harsh weather conditions (e.g., wind, cold, dryness). Currently, most of these can be considered only associations, because well-designed and controlled studies to establish a firm causative relationship are lacking.

HISTOLOGY OF THE LIP

Histologically, the lips are covered by three distinct epithelial surfaces. The external skin is keratinizing stratified squamous epithelium with a rich complex of hair follicles, sweat, and sebaceous glands located in the dermis, whereas the lip vermilion is composed of nonkeratinizing stratified squamous epithelium, adapted for external exposure. It remains smooth and dry, due to the paucity of glandular structures in the submucosal layer. Finally, the labial mucosa contains many serous, mucous, and mixed salivary glands in its submucosal layer, keeping the epithelial surface moist. Both the vermilion and labial layers are pink due to the presence of many elongated, vascular connective tissue papillae that project into the epithelial layer.

HISTOPATHOLOGY OF CANCER OF THE LIP

Squamous Cell Carcinoma

More than 90% of cancers of the oral cavity are of squamous cell origin. This cancer first appears as a nonhealing blister, recurrent crusting, lip induration, or an exophytic growth. Clinically, it may be impossible to distinguish

between actinic cheilitis and early squamous cancer, creating a low index of suspicion for biopsy. Three primary subtypes of SCC are identified in SCC of the lip: exophytic, ulcerative, and verrucous.

The exophytic form develops as an area of thickened epithelium that rises up from the surrounding tissue as it develops. With continued growth, there is a tendency for the base of the tumor to take on a saucer shape (**Fig. 12.1**). This base extends only a few millimeters under the epithelium, but externally, the lesion becomes heaped up upon itself extending outwardly a centimeter or more. Laterally, lesions may extend several centimeters with relative little invasion or metastasis.

Figure 12.1. SCC of the lower lip demonstrating exophytic growth.

The ulcerative type of SCC of the lip begins like the exophytic type, that is, as an epithelial thickening or blister. Ulceration usually occurs earlier and, in fact, may be present as a first symptom. As the lesion enlarges, it tends to take on a round or oval shape. Ulcerative carcinomas tend to bleed more easily than other subtypes. Further growth of the lesion tends to be more endophytic, displaying a relatively greater degree of invasion when compared

with a similar-sized exophytic tumor.

Verrucous carcinoma occurs rarely on the lips. It is a unique form of SCC in both its clinical behavior and morphology. Clinically, the lesion develops with a warty surface. Verrucous types are usually broad based and locally invasive. Histologically, they are well differentiated with few malignant features, save for invasion. The margins tend to push, and the integrity of the basement membrane is generally preserved. Biopsy of suspected verrucous carcinoma should include the full thickness of the lesion and a segment of adjacent uninvolved tissue. It is otherwise possible for the diagnosis to be confused with other forms of hyperplasia or hyperkeratosis as well as other SCC forms.

Basal Cell Carcinoma

Basal cell carcinoma is the second most common malignancy of the perioral region, accounting for 1% of cancers occurring in this region. These cancers occur with approximately equal frequency in both the upper and lower lips, but because of the infrequency of other cancers affecting the upper lip, basal cell carcinoma vastly dominate the total percentage of lesions of the upper lip.[6]

There has been considerable debate in the medical literature as to the actual existence of basal cell carcinoma arising from the vermillion portion of the lip. It is argued that the vermillion is involved only by direct extension of a lesion, which began periorally. Indeed, nearly all basal cell carcinomas found involving the vermilion are reported as arising from the cutaneous portion of the lip, at or near the mucocutaneous borer.

Melanoma

Melanoma may arise at the cutaneous, vermilion, or mucosal portions of the lip from melanocytes normally found in those sites. When arising from the lip vermilion, it is considered a mucosal melanoma subtype. Mucosal melanoma is most frequently found in the palatal or gingival mucosa and is found with less frequency in the buccal mucosa and vermilion. It presents as a smooth, black, or blue submucosal nodule that is covered by a thin, intact mucosa. However, before the diagnosis of a mucosal melanoma is accepted, careful screening of other body sites is required to confirm that it does not actually

represent a metastasis from a distant primary melanoma.[2]

PROGNOSTIC FEATURES ASSOCIATED WITH SQUAMOUS CELL CARCINOMA

Overall, carcinoma of the lip carries an excellent prognosis with 5-year survival rates reported at 79%.[2] The fact that most patients present with relatively small and early tumors is obviously an important factor in achieving this outcome. Even so, most of these cancers will have been present in some form for many months after home treatment with antibiotic ointment or skin creams has failed. But this delay is often offset by the fact that these cancers tend to be slow growing, tending toward more superficial lateral growth while remaining confined to the vermilion or immediate submucosal tissues until later in their course. A small percentage of patients will postpone evaluation until later in the course of the disease, by which time the cancer has grown to involve the musculature of the lip.

The size of the primary cancer is one of the most significant factors in predicting prognosis. That when tumors grow to a size larger than 4 cm (T3), the 5-year survival rates drop to 60%. Studies also consistently indicate that the rate of metastases increases with the size of the cancer; regional nodal metastasis has been found to be 5% for T1 lesions, 50% for T2 lesions, and 70% for T3 lesions.[7] When nodal metastasis occurs, 5-year survival is decreased to a reported rate of 40% to 80%.

Eighty percent of patients with perineural spread will have concomitant nodal metastasis. This further decreases 5-year survivor rates to 35%.[8] Although only occurring in 2% of patients, perineural spread requires special consideration for treatment and prognosis. SCC and other malignancies of the lip may invade the mandible by perineural spread along the mental nerve. Invasion of the maxilla can also occur via the infraorbital nerve. Classical clinical symptoms of perineural spread such as tingling, numbness, and pain cannot be relied upon as early indicators. Several cases have been reported with early spread along the inferior alveolar nerve extending to the cranial cavity, despite the lack of symptoms and a relatively small cancer.

MANAGEMENT OF CANCER OF THE LIP

A lesion of the lip that is nonhealing or in any other way suspicious for malignancy should be biopsied to obtain diagnosis. Once histopathologic verification is made, a treatment plan can be formulated. This must include curative management of the primary cancer and for any regional metastasis that may be present. Choice of treatment is made based on the preferences of both physician and patient, taking into account size, location, age, concomitant medical conditions, the likelihood that function of the lip and/or cosmesis can be preserved or restored, the relative ease of treatment delivery, and considerations of time and cost. A variety of therapeutic methods have been successfully employed in the treatment cancers of the lip, to include surgical excision alone, radiation therapy alone (external beam, or brachytherapy), or combined surgical excision and radiation therapy. Most studies have shown that surgery or radiation therapy produce similar cure and cosmetic results for small tumors.[9] These types of therapy are discussed below.

Radiation Therapy

Radiation therapy may consist of brachytherapy, external beam, or a combination of the two. Brachytherapy is a method of radiation therapy that employs the use of interstitial placement of radioactive implants. These are placed directly into the cancer and are carefully positioned to give a planned therapeutic dose to all parts of the cancer. Current practice favors the use of lower-energy radioisotopes such as iridium-192. First, hollow, nonradioactive needles are placed and checked radiographically for proper placement. The radioactive source is then placed. Placement of multiple needles during several treatment sessions may be required. It is important that accurate spacing of the needles be performed at each session, as overlapping of the radiation points creates problems of uneven distribution of the radiation. Brachytherapy has a reported local recurrence-free survival of 93% following treatment.[9] However, due to the complexities associated with brachytherapy, it has largely given way to external radiation, which is more versatile and controllable.

External beam radiation has become the preferred form of radiation therapy when treating lip cancers, particularly for tumors smaller than 1.5 cm. Treatment dosages typically vary from 5,000 to 7,000 cGy depending on the extent of the tumor and are generally fractionated over the course of 6 weeks.[7] Smaller daily fraction doses that are spread over a longer period generally result in fewer adverse long-term tissue changes, such as atrophy, fibrosis, and telangiectasia.

Treatment with either external beam or brachytherapy can be a very effective tool in the management of small (T1–T2) cancers of the lip. Radiation should also be considered to treat cancers of the lip that are relatively superficial but involve an area encompassing more than one-third of the lip. Cancers that involve the commissure and significant portions of either lip and cancers that are recurrent are also candidates for radiation therapy. The use of radiation requires that consideration be given when patients will return to high levels of sun exposure as the treated areas are more susceptible to further UV damage. Radiation may be an option for those patients who either refuse or otherwise cannot undergo surgery. Use of radiation requires that consideration be given when patients will return to high levels of sun exposure as the treated areas are more susceptible to further UV damage. Radiation therapy is frankly not appropriate for primary treatment of cancers with deep infiltration, perineural spread, or erosion of the mandible. Radiation is also not appropriate for use in large cancers where extensive tissue destruction has occurred, resulting in an anatomic deficit of the lip that will require surgical reconstruction.

The use of adjuvant radiation therapy has been shown to decrease recurrence rates following cases of close or positive margins following surgical excision. Cancers of the lip that are deeply invasive, especially those that involve the mandible or mental nerve or that have metastasized to regional lymph nodes, must be considered as a serious situation that require aggressive treatment. Surgical resection is usually necessary for curative treatment, but adjuvant treatment with radiation therapy may be considered for the treatment of locally advanced lip cancers (T4 and many T3).[7] Radiation therapy should be given serious consideration when cancer is recurrent, when there have been positive surgical margins, when there is perineural spread or extracapsular spread (ECS) of nodal metastases, or when tumors are poorly differentiated.

Surgery

Surgical excision, with histologic confirmation of tumor-free margins, is the primary preferred modality treatment of cancer of the lip. It allows for rapid treatment with immediate reconstruction of the lip. Surgery also allows for the taking of multiple tissue specimens from which the full scope of favorable or unfavorable histopathologic features can be assessed. Unlike radiation therapy, where negative effects of ionizing radiation are imposed on healthy tissues, the adjacent uninvolved tissues of the lip are affected only as mandated by acceptable surgical practice.

Any surgical procedure chosen for the management of cancer of the lip must focus on complete en bloc removal of the tumor with additional normal tissue at all margins of the resection. Anything less than this is oncologically insufficient and would likely result in treatment failure. Most surgical resections for primary cancer of the vermilion require some form of full-thickness excision of the involved portion of the lip. The most frequently selected configurations of excision are V shaped, W shaped, or rectangular. The converging lines of a V or a W excision must not be allowed to come too close to the lateral margins of the tumor. Cosmetically, it is ideal if the unit of lip resection can be confined to the borders of the anatomic lip unit, that is, mental crease or melolabial crease. Skin incisions should be planned to minimize the secondary deformity and facilitate reconstruction, but not at the expense of achieving margins negative for disease.

Effective surgical treatment involves not only eradication of the tumor itself but all of its microscopic extensions as well. Careful attention to the microscopic extensions leads to better local control of malignancy and, therefore, should be a primary goal of surgical treatment of lip cancer. Unfortunately, what constitutes an adequate margin to insure the removal of microscopic extension remains controversial. Detailed studies comparing the adequacy of various margin sizes during excision of cancer of the lip have not been performed. It is generally accepted, however, that a margin of 5 to 10 mm is adequate. Even when such margins are maintained, studies show that up to a 13% risk remains and that the final surgical specimen will display positive margins.[10] Thus, it is recommended that intraoperative frozen sectioning be performed with re-excision until clear margins are obtained.

Intraoperative frozen sections of the mental or infraorbital nerve may also

be necessary. If cancer cells are present at the infraorbital foramen, segmental resection of the maxillary bone may be indicated. The revised distal nerve stump is then biopsied to determine if further resection and/or other treatments are needed. Treatment of cancer, which encroaches on the alveolar process or the outer cortex of the mandible, should include a marginal mandibulectomy. However, actual invasion of the mandible requires generous segmental resection.

Management of the Neck

The management of regional lymph nodes in patients with cancer of the lip currently remains controversial. At initial presentation, SCC of the lip is associated with 15% rate of cervical metastasis,[11] the lowest among the subsites of the oral cavity. However, an additional 13% of patients will later develop cervical metastasis. The management of regional lymph nodes in patients with lip carcinoma, therefore, requires a thorough understanding of the patterns of lymphatic drainage system for comprehensive tumor assessment and effective treatment planning.

Metastasis of SCC and most other malignant tumors of the lip are almost always initially to the adjacent or regional lymph nodes, which reflects the known patterns of lymphatic drainage from the perioral region. Cervical metastasis from both the upper and lower lips occurs in a predictive orderly fashion. Cancers occurring in the upper lip metastasize first to the preauricular or infraparotid lymph nodes, followed by the submandibular nodes. Cancers of the lower lip tend to spread to the submental and submandibular nodes first, followed by the upper deep cervical nodes. Due to embryologic fusion planes, contralateral or bilateral metastases may develop in patients with lower lip cancers.

In patients with clinically palpable metastatic lymph nodes, cervical lymphadenectomy is appropriate. When metastasis is present in the parotid lymph nodes, a parotidectomy, with preservation of the facial nerve, should be done in conjunction with neck dissection. If metastases are confined to level I, the risk of level IV or V involvement is extremely low, and a supraomohyoid neck dissection is adequate. Ipsilateral neck dissection is sufficient if postoperative radiation is planned, to include the contralateral N0 neck. Such a strategy preserves the contralateral facial artery, which in turn will improve blood supply to local reconstructive flaps. Postoperative

radiation therapy is recommended for stage III or IV disease, recurrence, and ECS.

Generally accepted medical practice at this time dictates that neck dissection should be undertaken in oral cancers carrying a significant risk for occult cervical metastasis. T2 cancer of the lip, for example, carry an approximate 50% metastasis rate. On the other hand, T1 lesions carry a metastases rate of only 5%,[11] and therefore, neck dissection might not be mandated in the absence of other features. The presence of such aggressive features such as recurrence, perineural invasion, and poorly differentiated histology requires evaluation and consideration before a decision not to perform a neck decision is made. Bilateral supraomohyoid dissection should be considered when high-risk tumors involve the central portion of the lower lip. The functional and cosmetic consequences of supraomohyoid dissection can be kept to a minimum. If bilateral metastases are found, full bilateral neck dissection is indicated, normally with an attempt to preserve the internal jugular vein on at least one side. With cancer of the upper lip, an ipsilateral dissection of the superficial or lateral lobe of the parotid gland may also be indicated.

Adjuvant radiotherapy has been used for elective treatment of the neck in selected high-risk patients. It is often advisable following neck dissection with high-risk features, such as in the identification of multiple nodes or nodes with ECS. It should not, however, be considered a replacement for neck dissection because 54% of patients treated prophylactically with neck radiotherapy will go on to develop neck metastases within 2 years of treatment.[8]

The use of sentinel lymph node biopsy in the treatment of lip cancer has been reported, with promising results in a few small pilot studies.[12] As in other oral cavity sites, the lip readily lends itself to the identification of lymph node metastasis with this technique. Patients with large or poorly differentiated lip cancers are most likely the ones to benefit from this technique.

RECURRENCE

Recurrent cancer is most likely to present in the primary field, as regional lymphatic metastasis, or both. Recurrence at distant sites is extremely rare

once the primary has been locally and regionally controlled. Local recurrence of cancer of the lip following initial treatment with surgery or radiation ranges from ~5% to 25% overall and is the most common form of treatment failure. As would be expected, the rate of local recurrence tends to increase proportionately with the size of the original cancer. The specific involved subsite has been associated with varied chances for local recurrence. The highest incidence has been noted with cancer of the commissure, and the lowest with cancer of the lower lip.

Recurrence of cancer of the lip is best managed with aggressive surgical resection, incorporating the use of intraoperative margin assessment to assure complete clearance of the tumor. Because up to one-fourth of patients presenting with cancer of the lip will present with subsequent cervical lymph node metastases, strong consideration to elective neck dissection should be considered. Except in cases of bone involvement, local recurrences of cancer of the lip should not be expected in 60% to 85% of cases where appropriate surgical management techniques have been employed.[12] The salvage rate is considerably lower if the local recurrence is associated with cervical lymph node metastases.

RECONSTRUCTION OF THE LIP

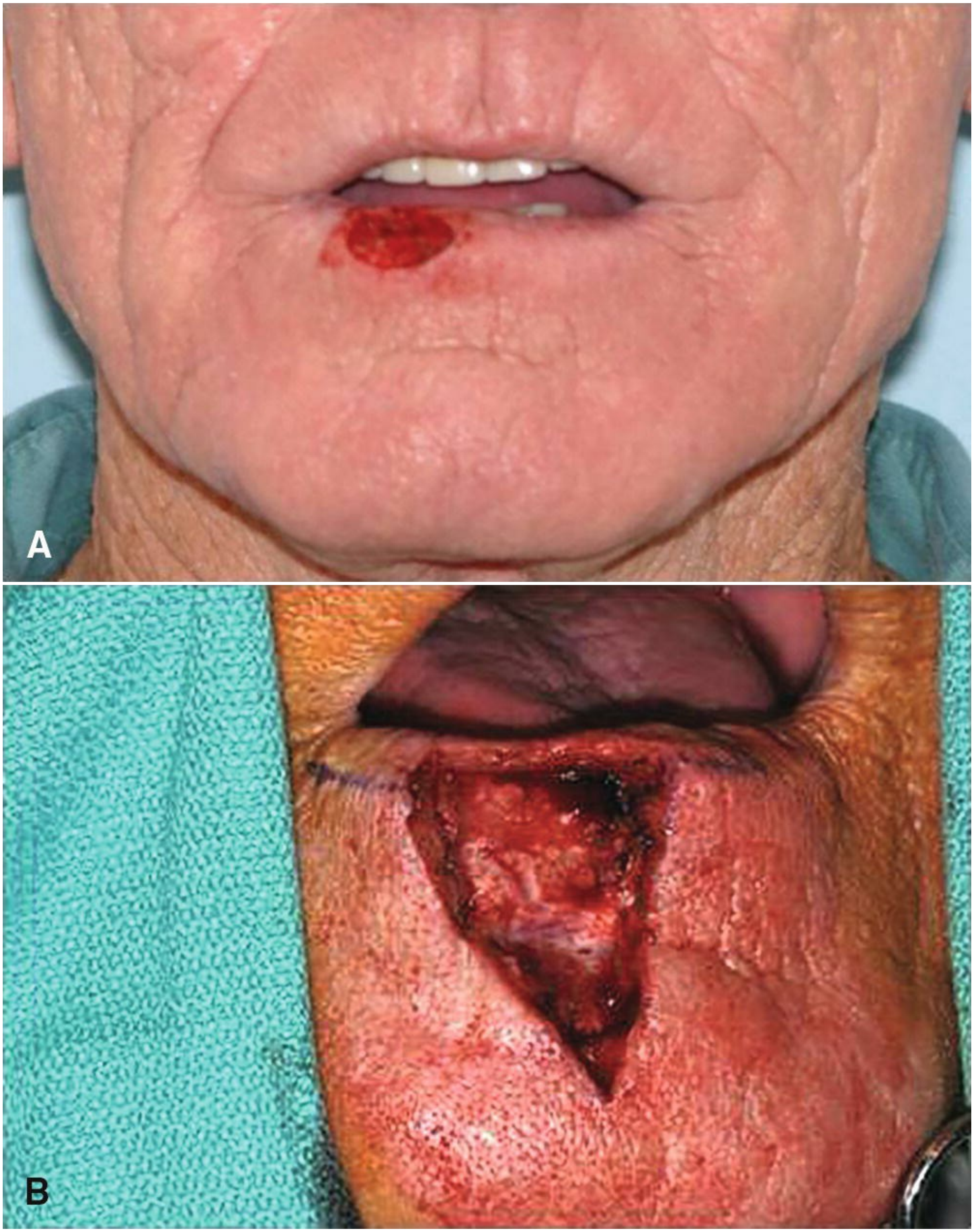
The treatment of cancer of the lip can result in a variety of defects, ranging from small superficial deformities treatable with primary closure to larger deformities requiring free tissue transfer. Regardless, the goals of reconstruction remain to restore oral competence, maintain oral opening, and achieve an aesthetic result that approaches normal appearance. For adequate function of the lip, it is best if continuity of the orbicularis muscle sphincter can be restored in some fashion, particularly in the lower lip. Aesthetically, it is best if all incisions can be placed along the peripheral borders of the lip unit (mental and melolabial creases) or parallel with the lines of relaxed skin tension of the lips.

When approaching reconstruction of the lip, one should first assess the lesion and attempt to determine the amount of mucosa, muscle, and skin that will be required. Accurate assessment of three-dimensional tissue loss and required volume for reconstruction is paramount to the success of reconstruction of the lip. The effect of lip defects upon facial appearance will

be exaggerated as a result of the displacement of wound edges by the lateral pull of the facial muscles. These defects can be divided into vermilion-only defects, defects that involve less than one-third of the total lip length, defects that involve between one- and two-thirds of the total length of the lip, and finally total lip defects.13

Vermilionectomy or “lip shave” is an indicated treatment of carcinoma in situ and actinic cheilitis. Defects isolated to the vermilion may be approached with healing by secondary intention, direct primary wound closure, and mucosal advancement flaps. Healing by secondary intention is appropriate for small superficial defects confined to the vermilion. Small defects, which do not distort the remaining vermilion or lip contour, are amenable to primary closure, although this technique may lead to unsightly bunching of the remaining vermilion. More commonly, the resulting defect is large enough to require an advancement flap of the labial mucosa. Dissection for this flap is done in the submucosal plane toward the gingival buccal sulcus. Two back cuts at each commissure toward the gingival buccal may be required to facilitate advancement. Neural and vascular connections can be preserved and stretched forward with the advancing flap, optimizing sensory function for the restored vermilion. Occasionally, the mucosal flap is of insufficient bulk to accomplish a desired result. In such cases, a pedicled orbicularis oris can be rotated into the base of the defect to improve cosmesis.

Generally, defects involving less than one-third of the horizontal length of the lip can be closed primarily. The length of the lower lip horizontally measures 7 to 7.5 cm allowing primary closure of a defect of up to 2.5 cm. The lip lends itself well to primary closure due to its remarkable tolerance for stretching. Small cutaneous defects can usually be closed in routine fashion with fusiform closure, whereas full-thickness defects benefit from wedge-shaped closure (**Fig. 12.2**). The long axis of either closure should be oriented parallel with relaxed skin tension lines leading to a more obliquely oriented flap in the lateral portions of the lip. M-plasty is often helpful to allow avoidance of crossing subunit borders and prevent alar or vermilion distortion. For full-thickness defects, the mucosa is reapproximated first, followed by the muscle layer, and finally the skin, with an emphasis on precise reapproximation of the vermillion. Re-establishment of the vermilion border is essential because even minute misalignment is easily recognizable.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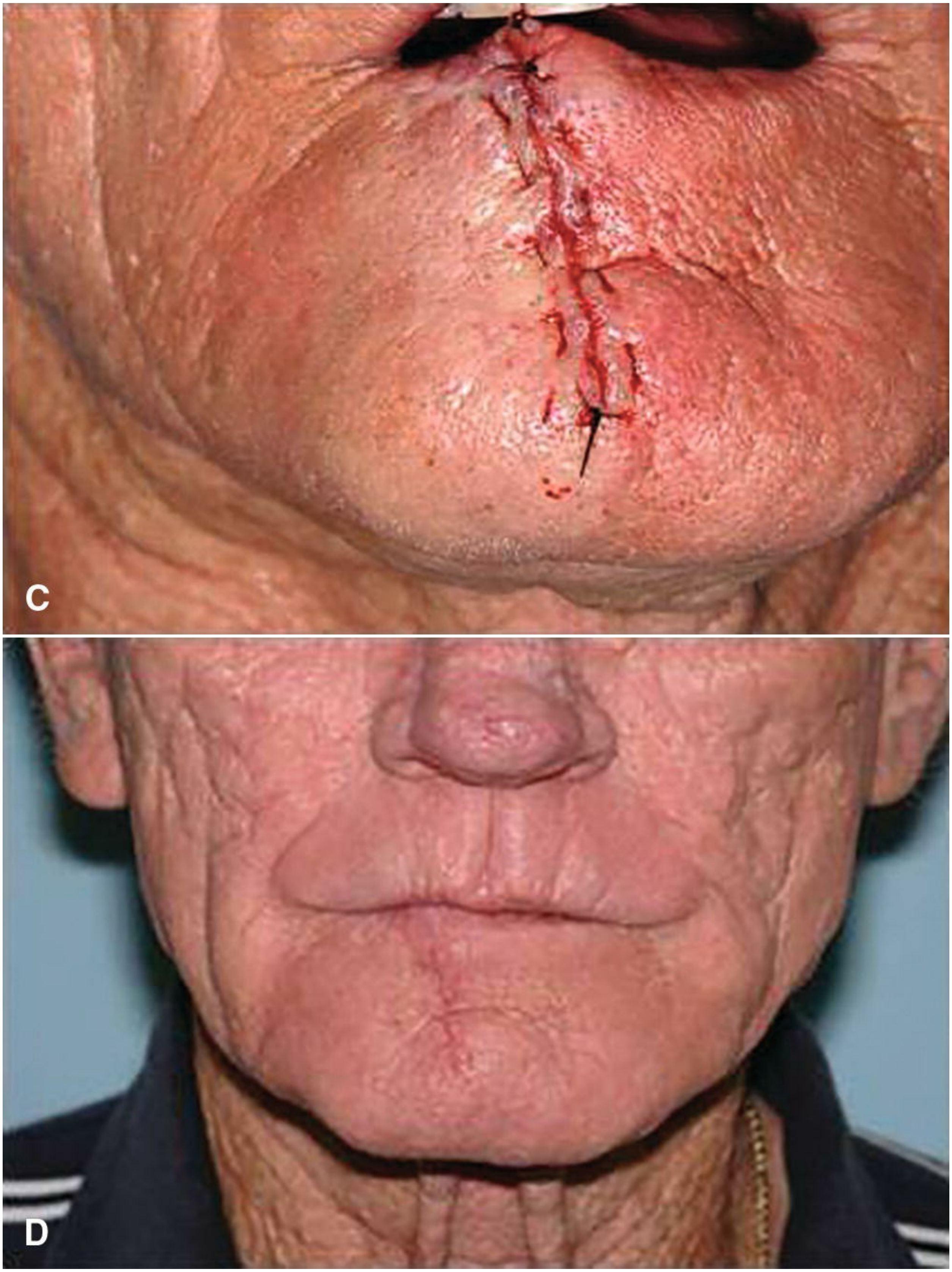

Figure 12.2. Defects involving less than one-third of the horizontal length

can be closed primarily. **A:** Lesion involving 25% of the lower lip. **B:** Converted to a wedge shape to aid in closure. **C:** Appearance following wound closure. **D:** Result 4 months following wedge excision and primary closure.

The cheeks and, less commonly, the chin are the natural sites to obtain additional tissue for lip reconstruction. A large variety of techniques have been described that transfer tissue from these areas into the lip. The most commonly chosen method involves transposition of skin and subcutaneous tissue from the melolabial fold, using a pedicle that is either superiorly or inferiorly based. The melolabial flap is designed so that the donor site, as it is closed, is well hidden within the melolabial crease. The use of a superiorly based pedicle tends to cause greater cosmetic detraction because it disrupts the medial portion of the melolabial crease—a situation that can be improved later by placing an incision across the pedicle in a fashion that restores the full line of the crease. Melolabial transposition may be used for cutaneous resurfacing of the lip and in some situations for full-thickness lip deficits (**Fig. 12.3**). It is not capable of truly restoring the orbicularis muscle but rather relies on a certain degree of tightness. It is therefore less ideal in full-thickness reconstruction of the lower lip. Surfacing for the underside of these flaps may be done either with a second flap, including the skin or oral mucosa, or with application of a graft of skin or mucosa. A skin graft can be buried beneath the cheek flap in a "delayed" fashion for 2 to 3 weeks, allowing the combined tissues to be later transferred as a composite. Defects greater than one-third, but less than two-thirds of the horizontal lip, are ideally reconstructed with pedicled or tissue flap rotated from the opposing lip. In general, this corresponds to defects between 2.5 and 4.5 cm in length. The majority of the reconstructions of this size are achieved with the aid of an Abbe cross-lip flap, an Estlander cross-lip flap, or a Karapandzic flap.

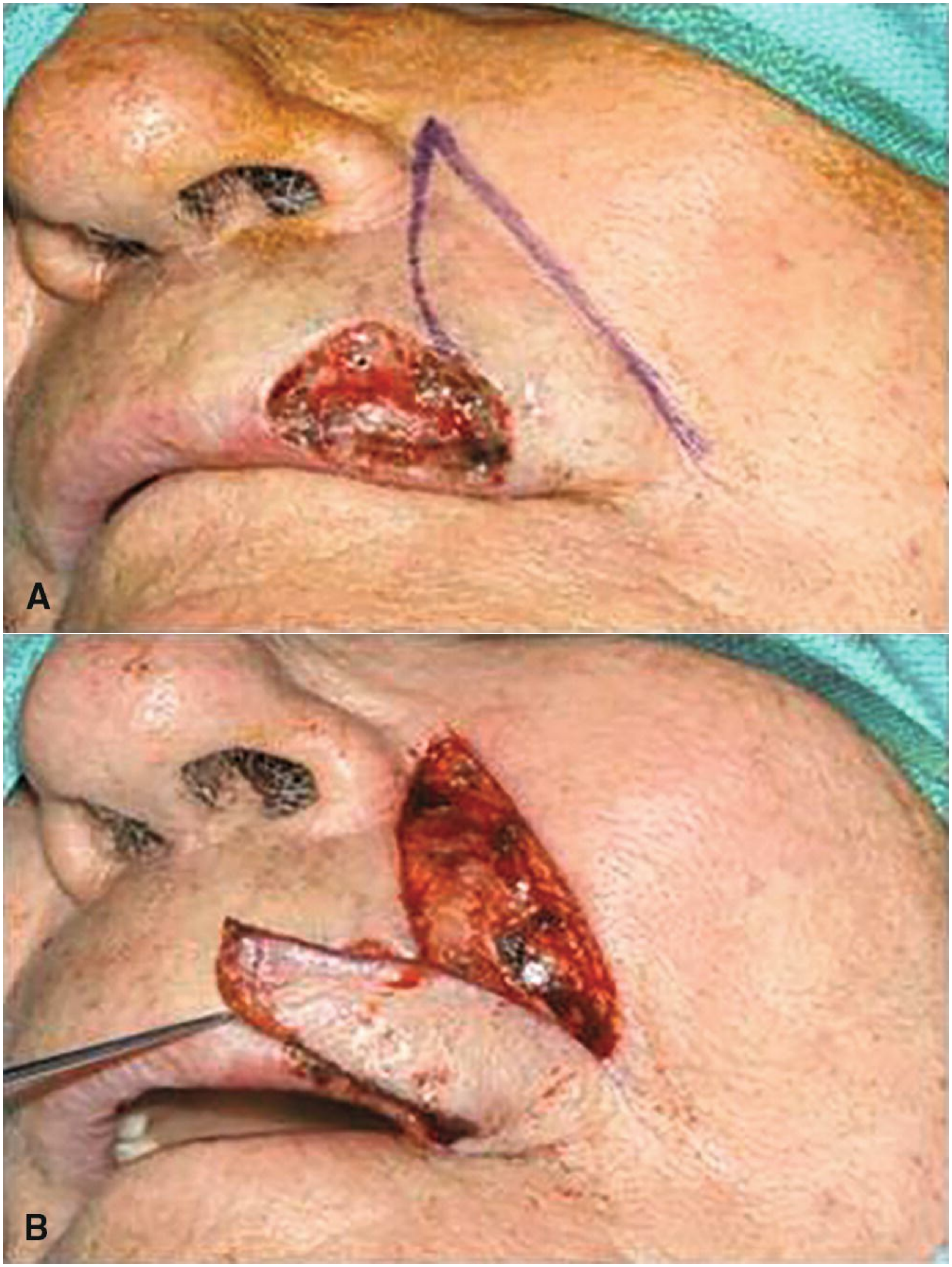
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Figure 12.3. Melolabial transposition may be used for cutaneous resurfacing of the lip. **A:** Intraoperative design of melolabial transposition flap. **B:** Partial-thickness island of tissue rotated to fill the defect. **C:** Appearance following flap inset and closure.

Both Abbe and Estlander flaps use full-thickness tissue transferred from opposing lips pedicled on the labial artery. They differ in that the Abbe flap is used for defects medial to the oral commissure. An Abbe flap is usually designed in a wedge shape and is kept viable through a small pedicle containing the labial artery, which extends across the oral commission (**Fig. 12.4**). The pedicle is released during a second procedure 2 to 3 weeks later (**Fig. 12.5**). In a single-stage procedure, donor tissue is rotated around the oral commissure to the opposing lip (**Fig. 12.6**). This technique typically results in blunting of the commissure angle and may require a commissuroplasty at a later date.

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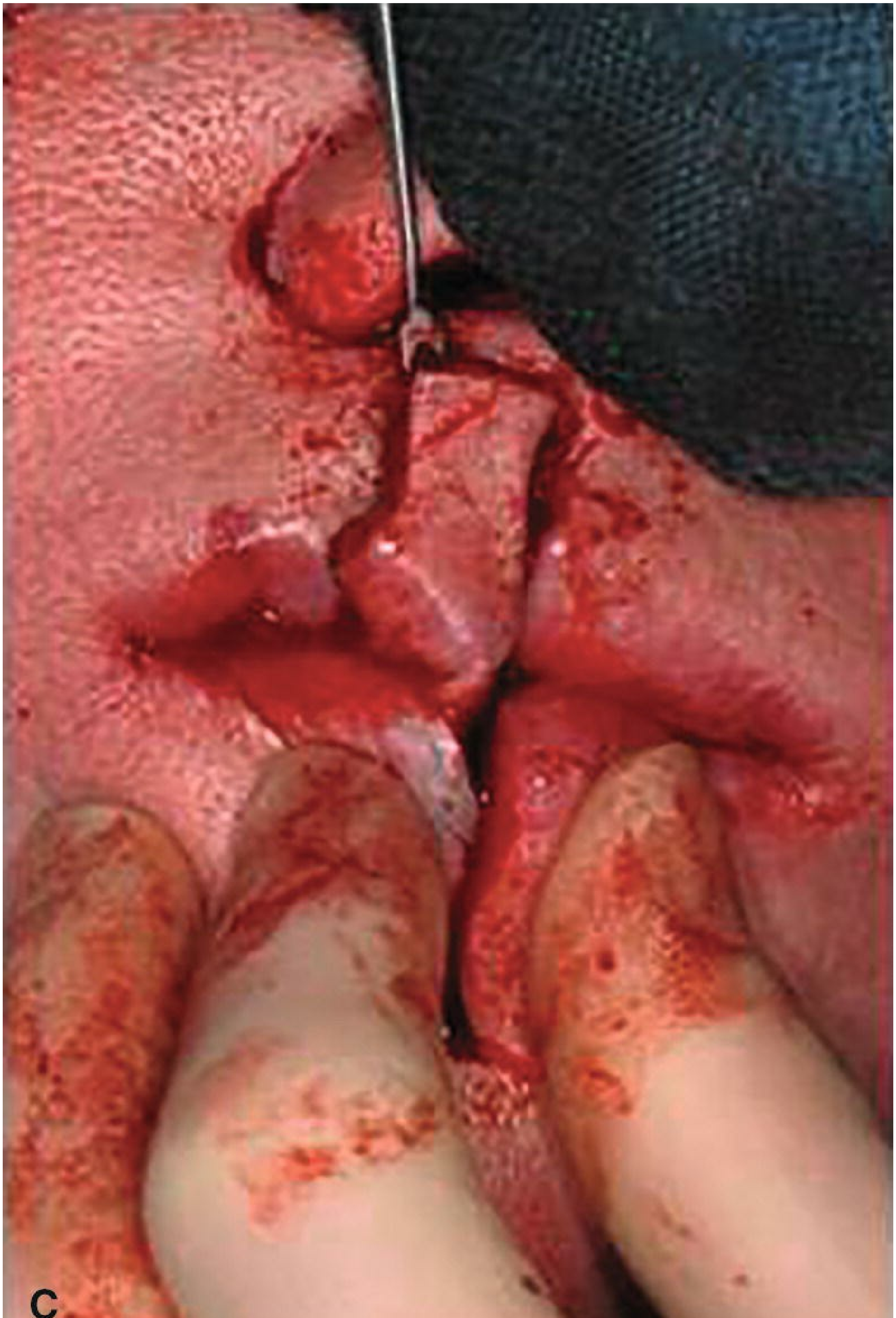
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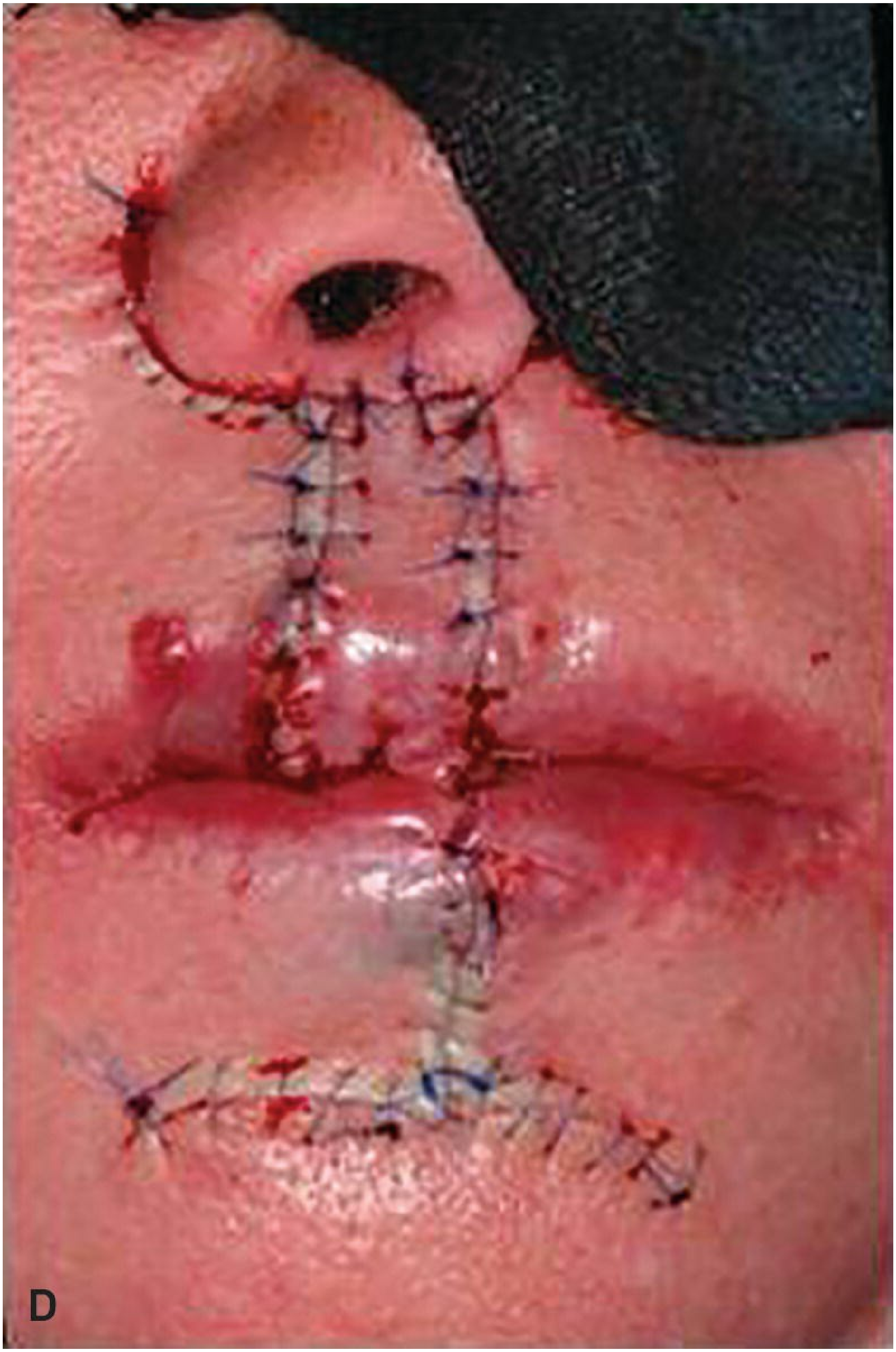
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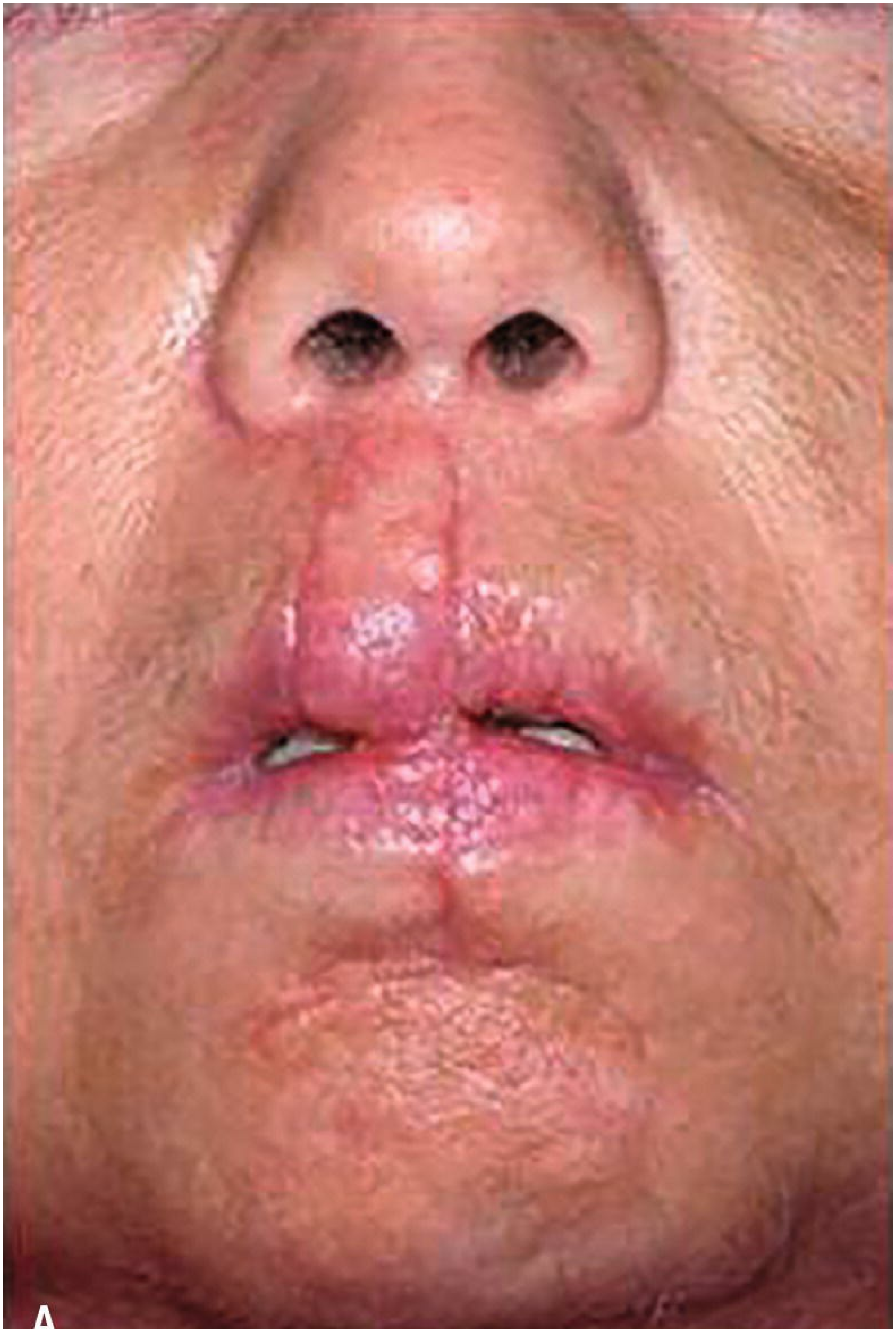
Figure 12.4. Abbe cross-lip flap may be used to repair defects of the central lip. **A:** Central lip wound following excision of tumor with design of flap. **B:** Full-thickness incisions performed while maintaining a small pedicle, which contains the labial artery; **C:** Donor flap rotated to the upper lip. **D:** Abbe cross-lip flap following closure.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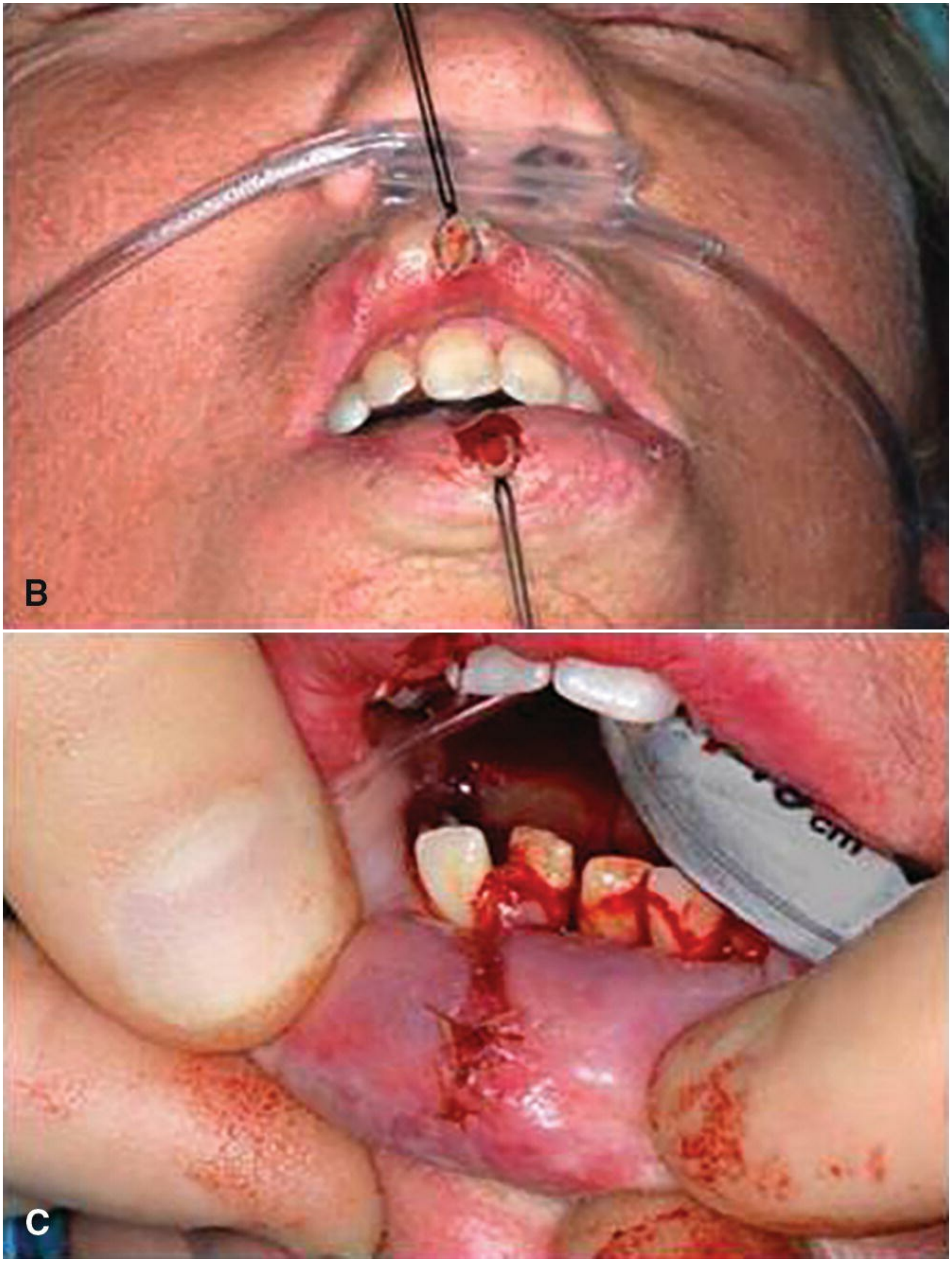
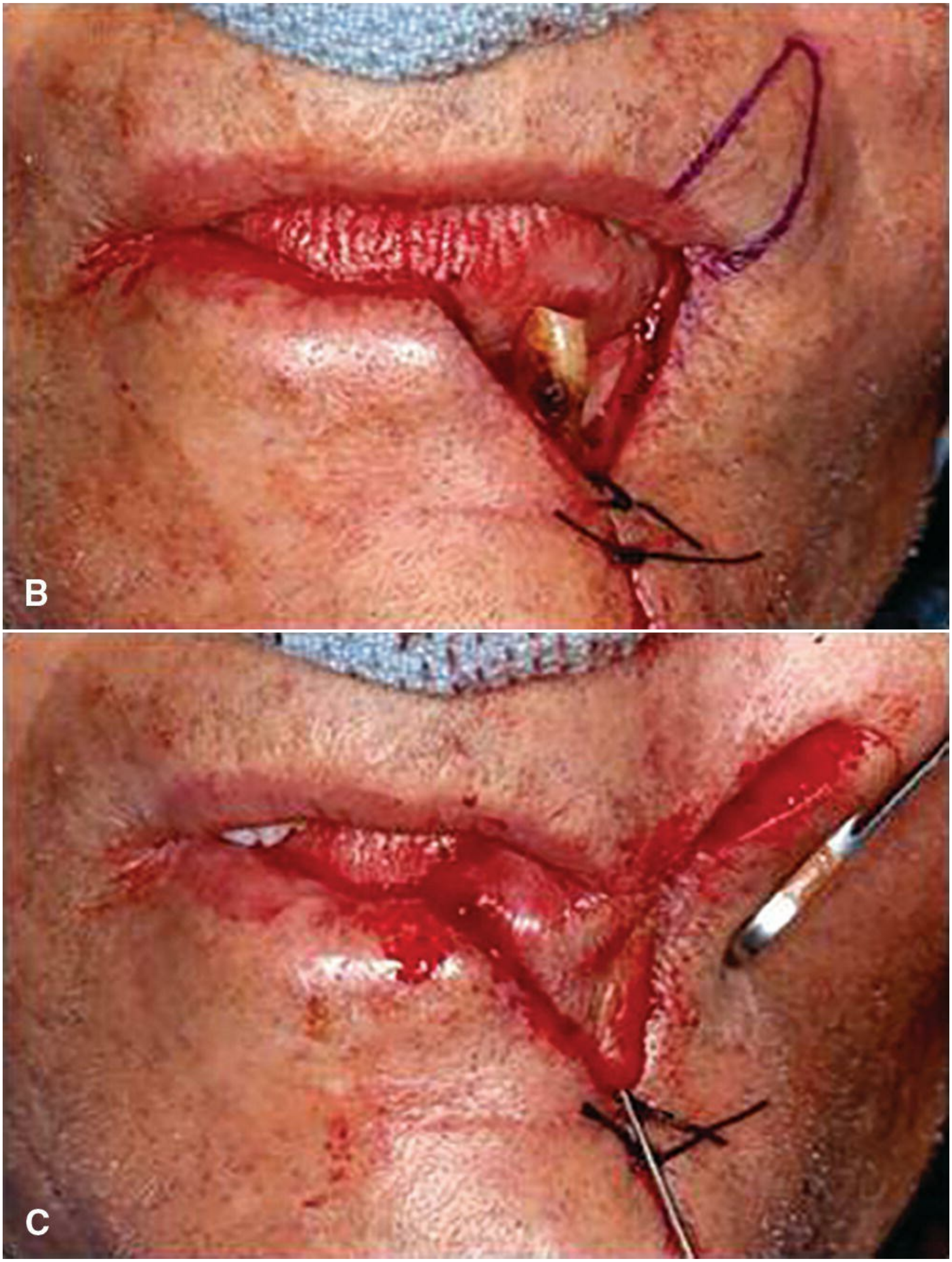


Figure 12.5. Abbe cross-lip flap requires second stage for flap division. **A:**

Appearance of Abbe cross-lip flap prior to takedown of pedicle. **B:** Pedicle divided. **C:** Following division of the pedicle lip is repaired with primary closure.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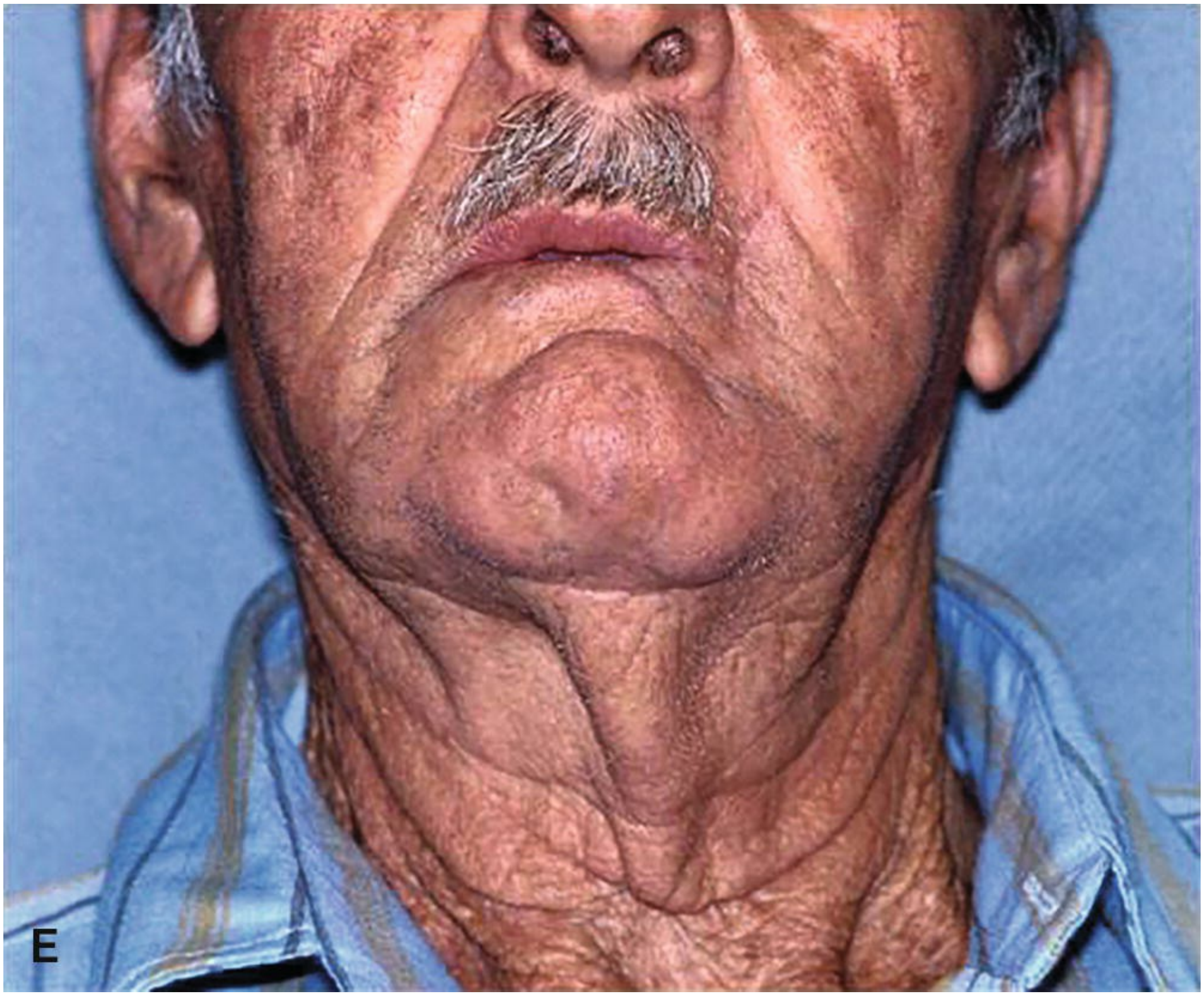


Figure 12.6. Estlander cross-lip flap utilized for closure of lateral lip defects. **A:** The anticipated resection is marked out. **B:** Defect involving the lateral third of the lip is shown with designed Estlander flap. **C:** Tissue from the upper lip rotated inferiorly while maintaining small pedicle containing the labial artery. **D:** Estlander flap following onset. **E:** Long-term results following reconstruction win an Estlander flap.

Traditionally, both flaps are designed with the same height as the defect and half the width. This results in a decrease in length of the donating lip, proportional to the increase of the received lip. It is particularly important to ensure that the full vertical height of the defect is replaced with the transposed tissue. Asymmetry of the horizontal length is easily overlooked, but even minor elevations in vertical height draws attention.

Although originally described with a wedge shape, cross-lip flaps may be

also designed in a rectangular or M shape when desired. Both Abbe and Estlander flaps also lend well to combinations with other forms of reconstruction, and multiple cross-lip flaps may be used simultaneously. The biggest drawback to the use of cross-lip flaps is the total denervation that occurs as they are transferred; however, some motor and sensory function will generally redevelop over the course of several months to a year.

The Karapandzic flap is a circumoral advancement technique that preserves the vascularity, sensation, and the function of the remaining orbicularis oris muscle. It is designed by making circumoral skin incisions around the peripheral margins of the lip, starting, when possible, within the mental or melolabial creases (**Fig. 12.7**). As the incisions approach the vicinity of the oral commissure, however, the Karapandzic flap should be extended out to the surrounding cheek because the melolabial crease closely approximates the commissure. The muscle is then released as necessary to allow for advancement by spreading parallel to the muscle fibers (**Fig. 12.8**). The integrity of the neurovascular supply and muscle fibers of the orbicularis oris muscle is thereby preserved, which results in good functional and aesthetic outcomes. Blunting of the oral commissure does occur. Because it occurs bilaterally, however, it is usually of little significance. However, the degree of resulting microstomia created can be limiting, especially in patients who wear dentures.


A

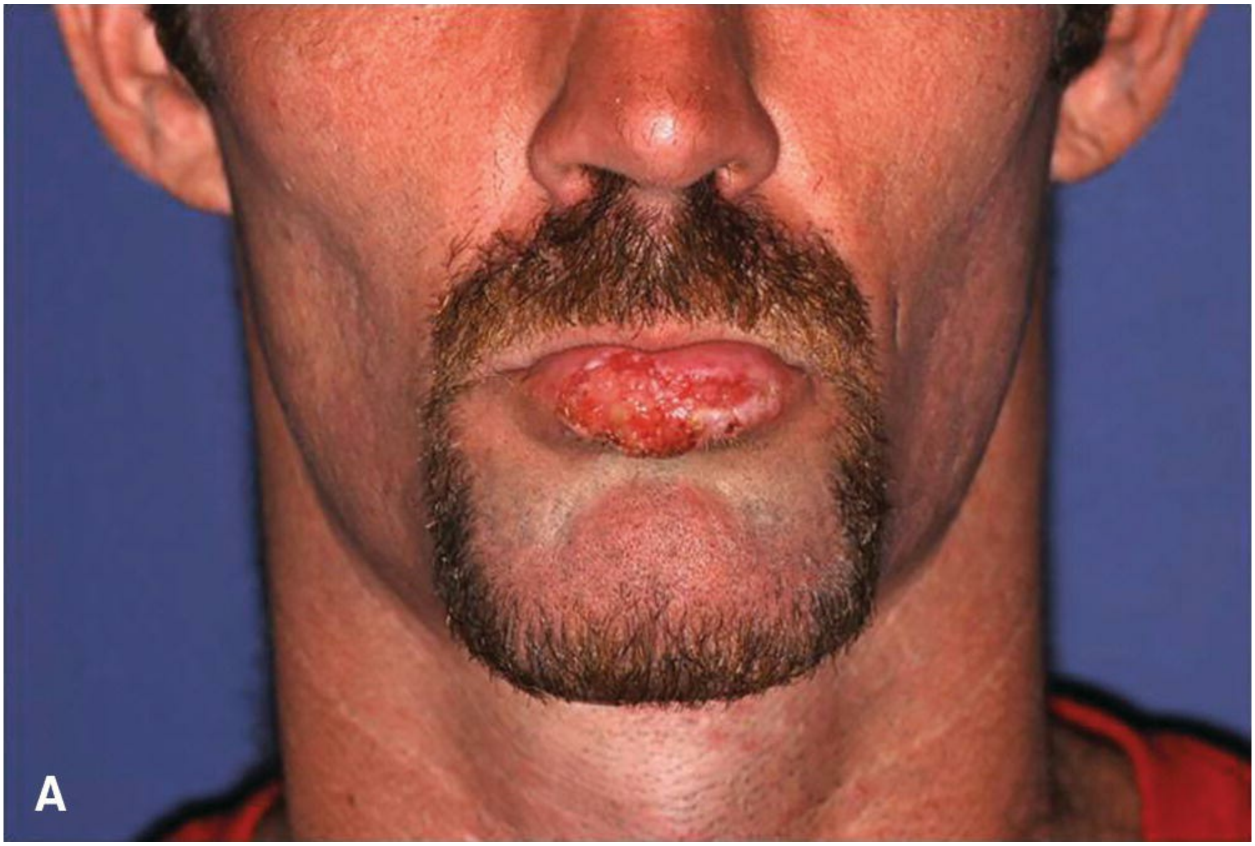

B

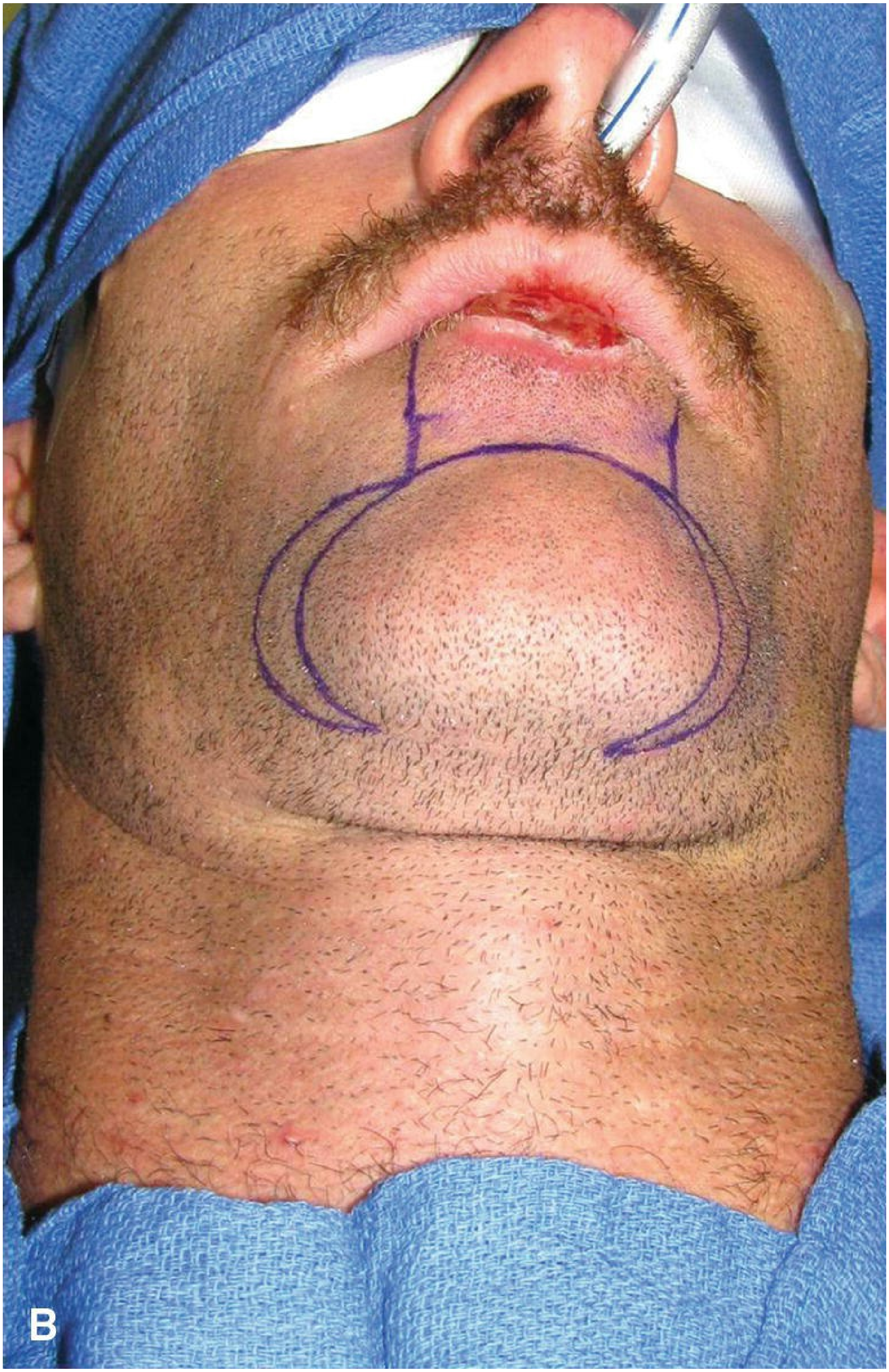
Figure 12.7. The Karapandzic flap is performed with circumoral advancement. **A:** Lesion involving central half of lower lip. **B:** Full-thickness defect following resection of the tumor with planned circumoral rotation. **C:** Closure of Karapandzic flap.

Figure 12.8. Preservation of muscle fibers and neurovascular supply while performing Karapandzic flap.

In the mid-19th century, Bernard and von Burow separately described a method for reconstruction of full-thickness defects, which are larger than two-third of the lip. It involves direct medial advancement of tissue from the cheeks, which is facilitated by removal of strategically placed triangles of skin that allow for a more even redistribution of the facial tissues. This concept of reconstruction is often referred to as “Bernard cheiloplasty,” and von Burow’s eponymous credit comes with the term “Burow triangle.” The procedure was originally done with full-thickness incisions but was later modified to minimize disruption of the facial musculature. Overall functional and cosmetic results with this reconstruction are typically only fair because satisfactory restoration of the orbicularis sphincter is often difficult to achieve.

Several modifications of the Bernard cheiloplasty have been described in attempt to produce more favorable scars and better muscle function. Most notably, Webster's modification (**Fig. 12.9**) moved the Burow triangles laterally, resulting in a scar that lies entirely within the melolabial fold. The excised triangles are partial thickness only, thereby preserving the neurovascular supply to the orbicularis oris and buccinators muscles. This technique can be used to restore near-total loss of the lip and may be adapted for reconstruction of either the upper or the lower lip. Webster made a further refinement for upper lip reconstruction, with the perialar crescent advancement flap (**Fig. 12.10**). This flap uses incisions placed within the alar crease and includes the removal of crescent-shaped areas of cheek tissue adjacent to the alae. This prevents deformity of the alar base, lip, and oral commissure by preserving the alar crease. The perialar crescentic advancement flap works well for defects of the upper cutaneous lip, especially those located immediately inferior to the nasal sill.

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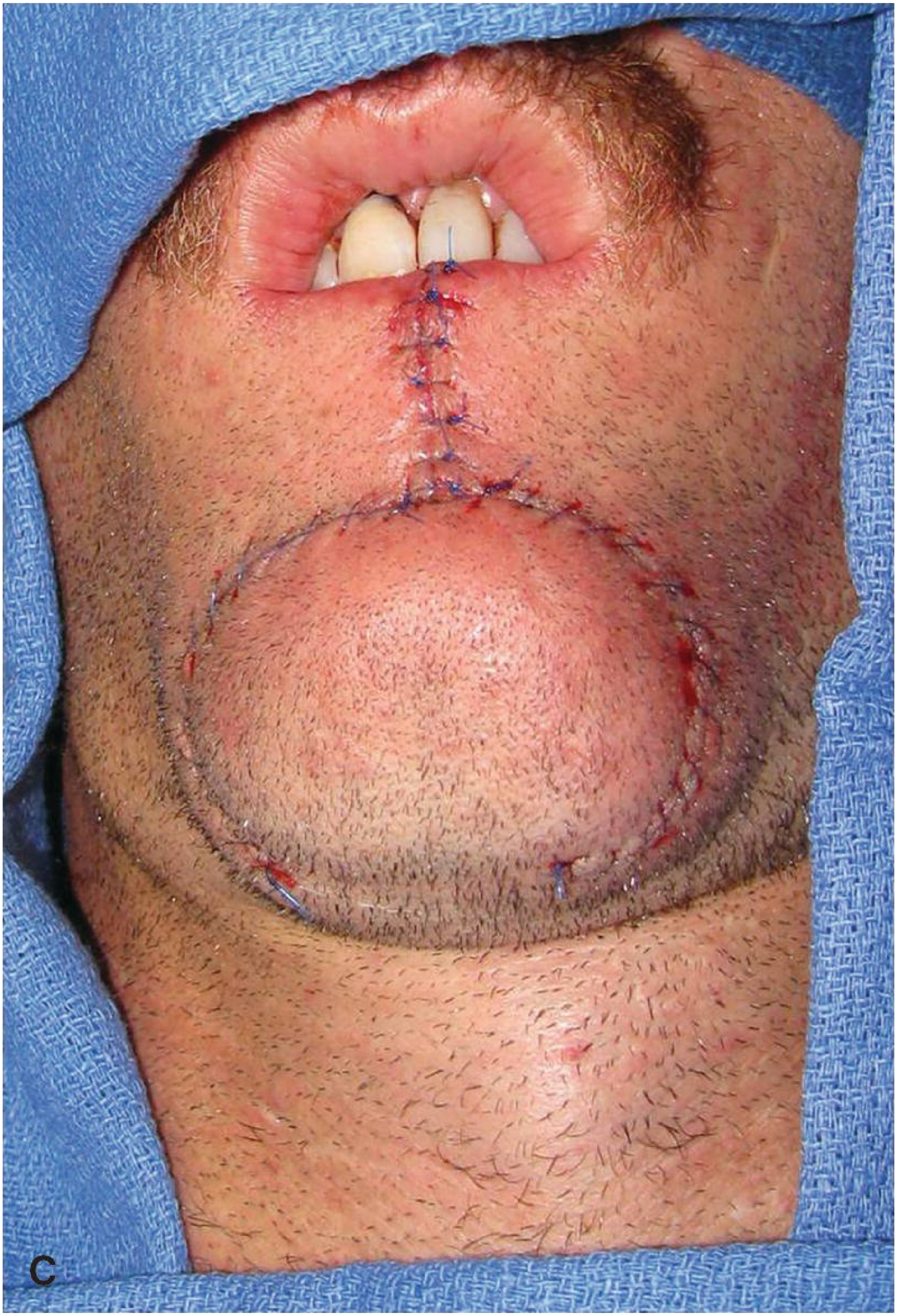
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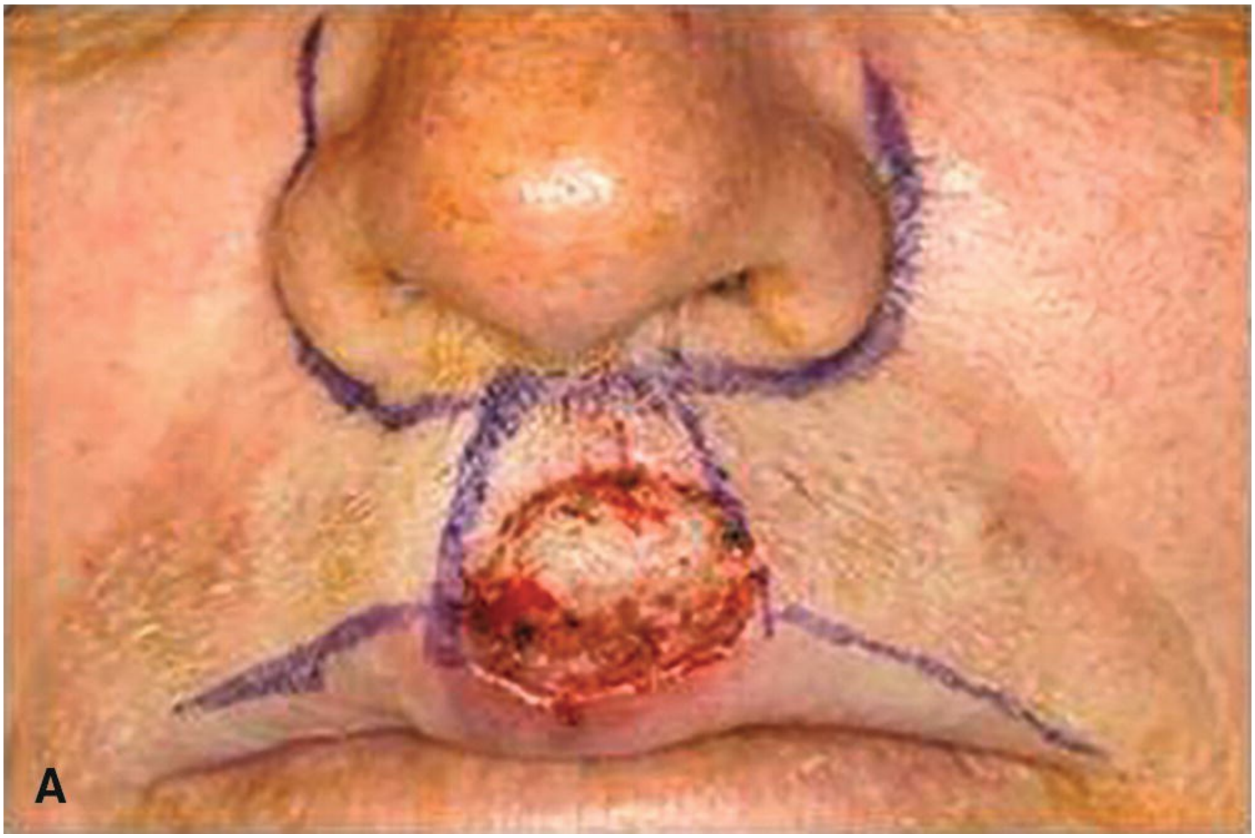
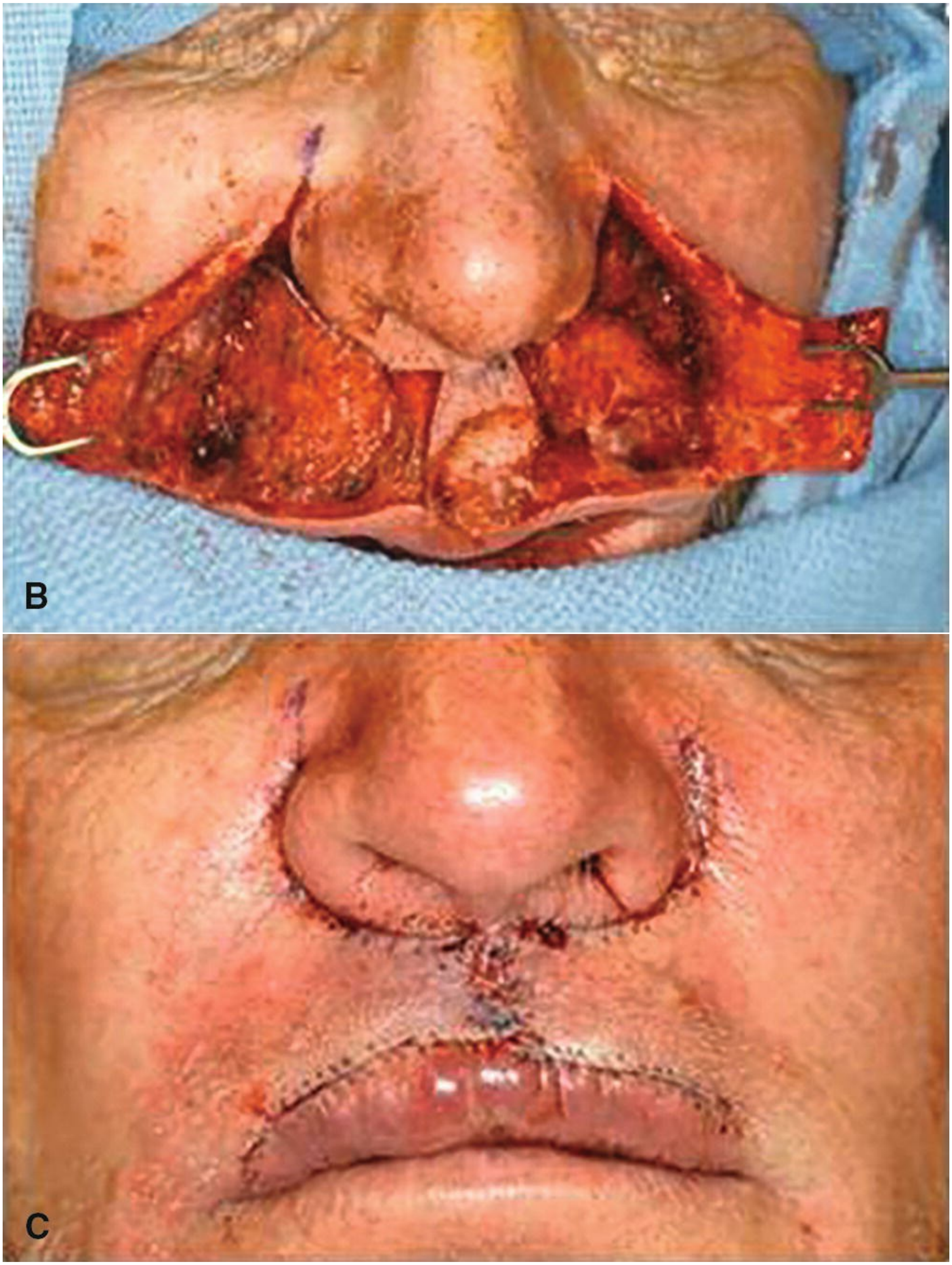
Figure 12.9. Lesions involving greater than two-thirds of the lower lip benefit from reconstructions using modifications of the Bernard cheiloplasty. **A:** Lesion involving 75% of the lower lip. **B:** Anticipated area of excision with planned Burow triangles. **C:** Closure with modified Bernard cheiloplasty.

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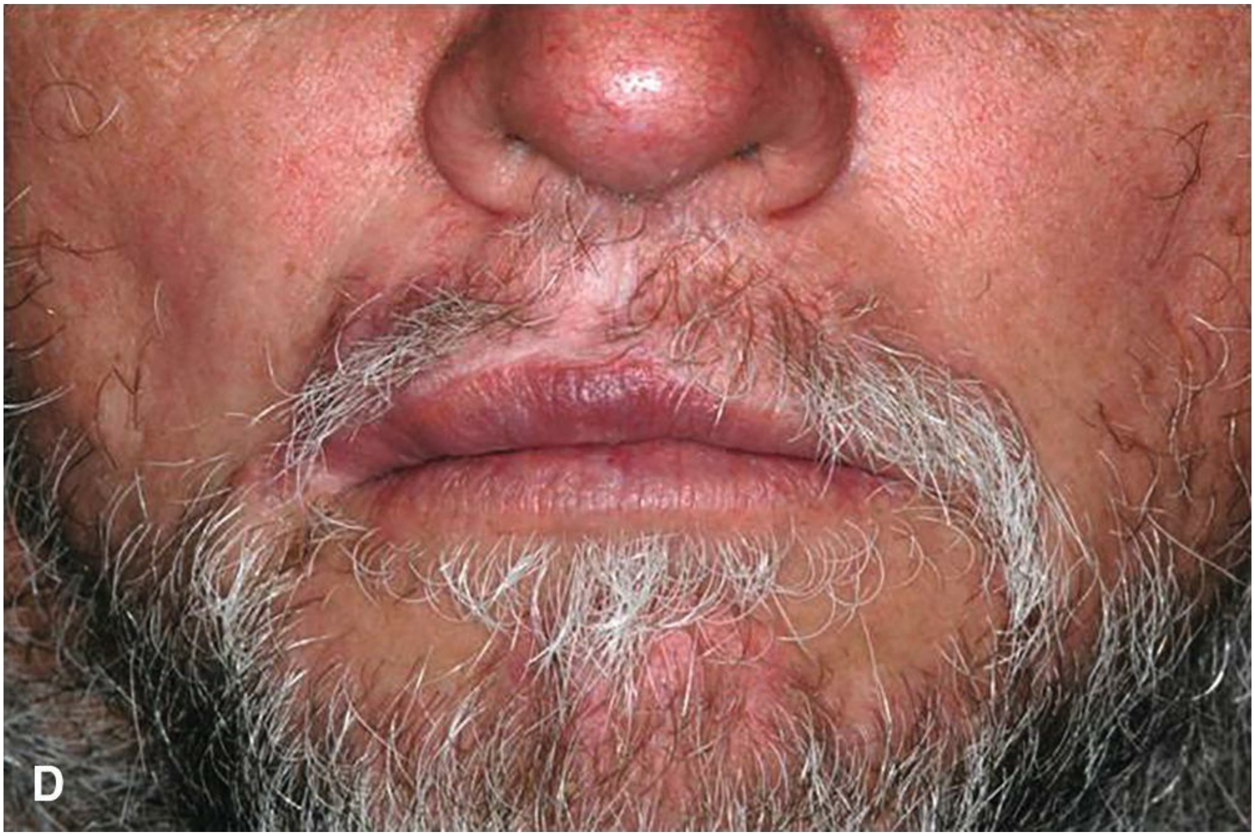
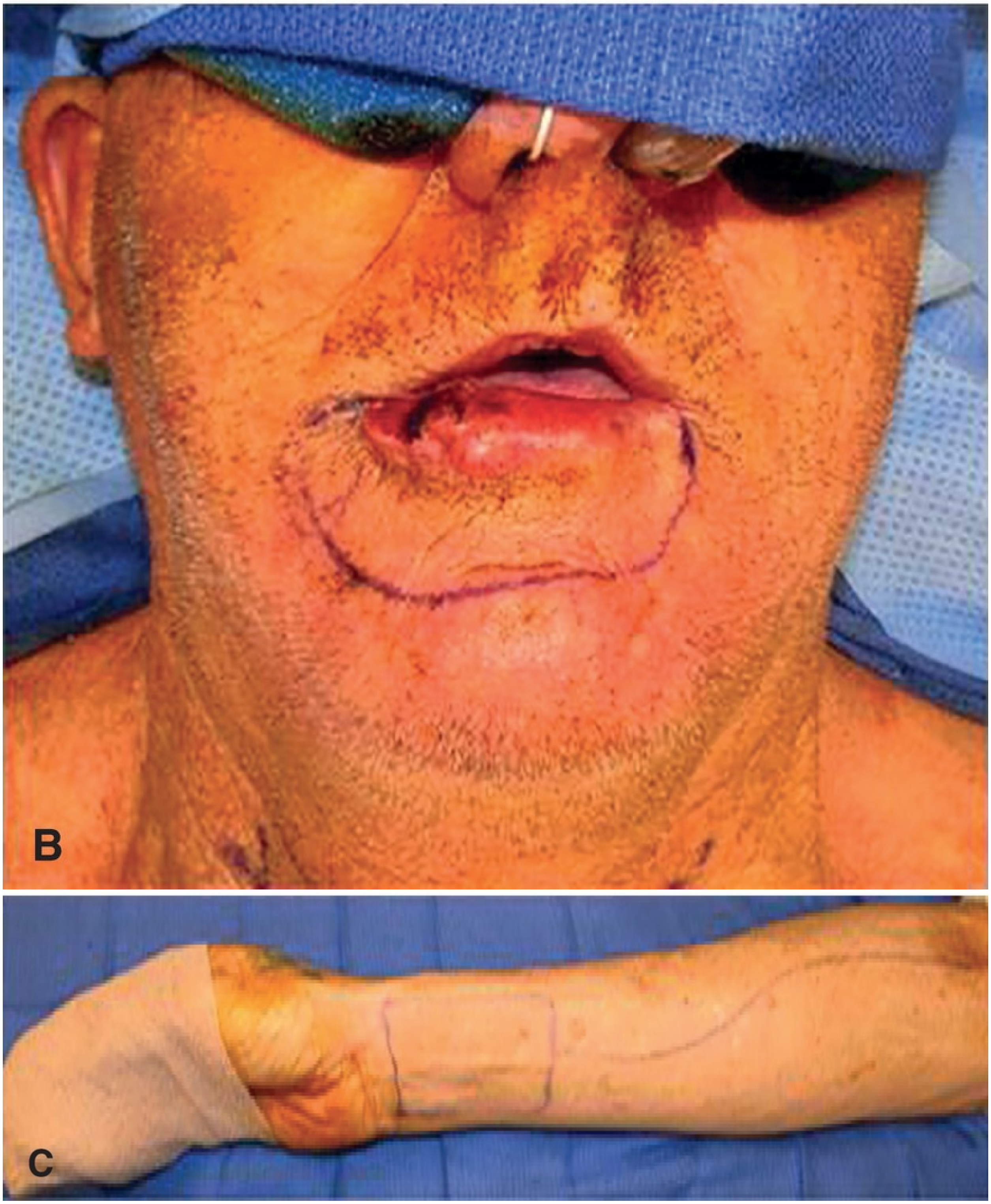


Figure 12.10. The perialar crescentic advancement flap is best suited for defects of the upper cutaneous lip. **A:** Lesion midline of the upper lip with Burow triangle marked act. **B:** Central-thickness incisions and subcutaneous flaps elevated to preserve neurovascular supply. **C:** Bilateral perialar crescent advancement flap closure. **D:** Long-term results following perialar crescent advancement flap.

Reconstruction of total defects of the lip is a challenging problem. Not only do the internal and external lining have to be replaced, but oral competence needs to be restored. In such cases, the rotation of large amounts of local tissues may lead to further facial disfigurement, and microstomia. These issues, however, can be overcome with microvascular reconstruction, which allows for single-stage reconstruction of such defects that include surrounding affected areas such as the cheek or chin. Additionally, if there is bone involvement, the mandibular arch can be reconstructed with the use of an osseofasciocutaneous flap.

The most commonly used microvascular free tissue transfer is the radial forearm flap. The radial forearm flap was initially described by Sakai et al. in

1989.[14] For reconstruction of the lip, it carries the advantages of being relatively easy to harvest, has a long pedicle length, and provides a good color match and pliable skin paddle (**Fig. 12.11**). The radial forearm free flap is based on the radial artery with its venae comitantes. The proximity of the facial vessels to the resection makes them ideal for use in revascularization. They are of adequate caliber and readily accessible at the angle of the mandible. For an anastomosis at this level, a pedicle length of approximately 8 cm should be sought.[15] It can also be harvested with the lateral antebrachial cutaneous nerve, providing sensation to the reconstructed site. This addition can play an especially important role in patient rehabilitation as the sensation of drooling aids in the rehabilitation of a competent oral stoma.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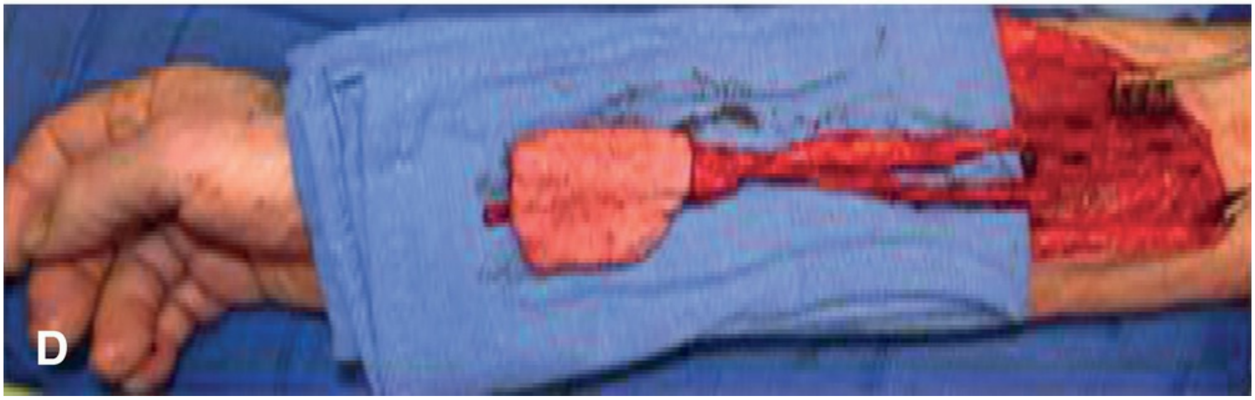
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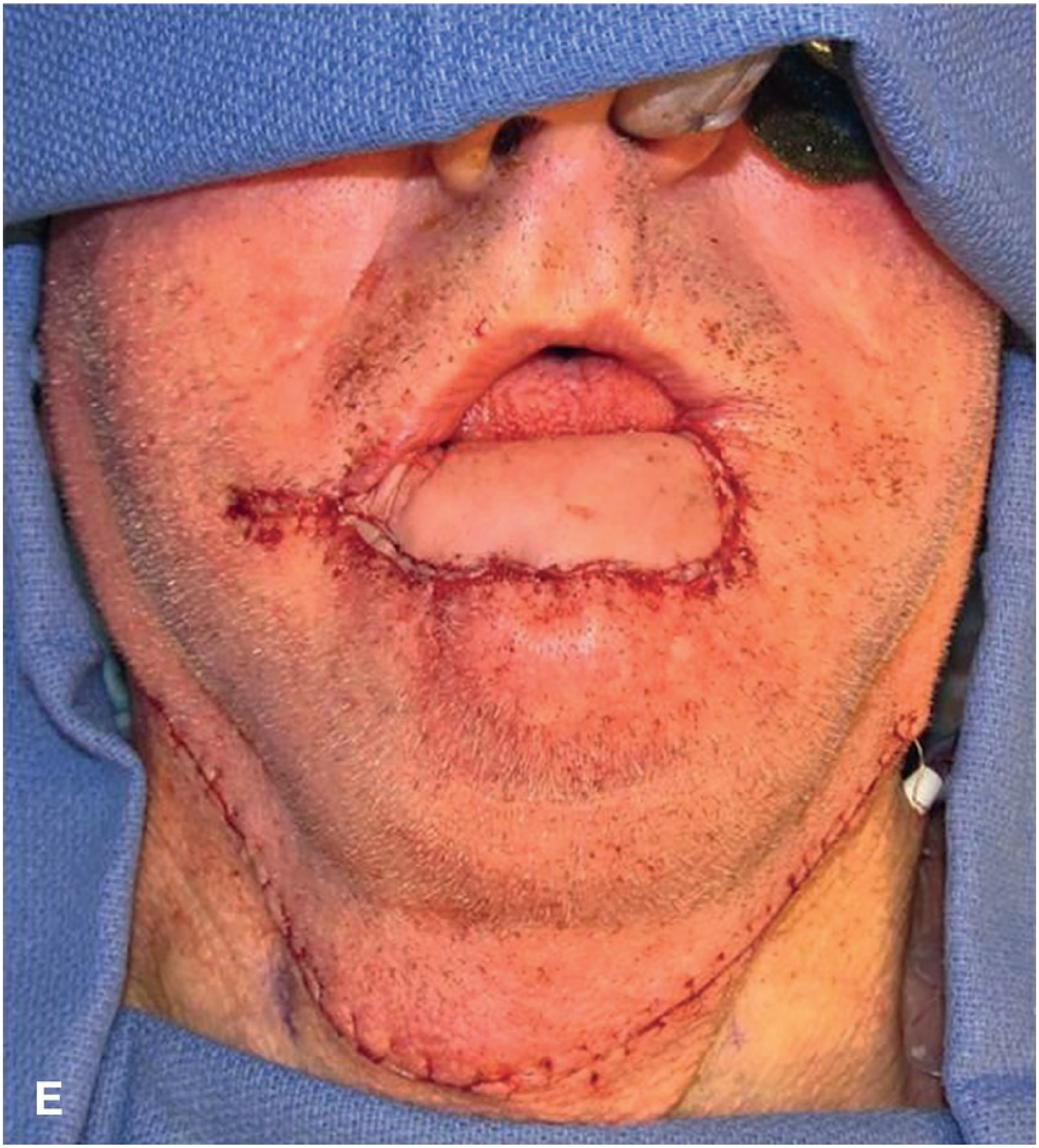
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Figure 12.11. Free flap reconstruction aids in reconstruction of total lip defects. **A:** SCC involving the entire lip. **B:** Anticipated area of resection. **C:** Skin markings for radial forearm free flap. **D:** Radial forearm free flap pedicled to radial artery, venae comitantes, and cephalic vein. **E:** Radial forearm free flap following inset for reconstruction of total lip defect. **F:** Patient 5 weeks following radial forearm free flap reconstruction of total lower lip defect. **G:** Postoperative demonstration of mouth opening following radial forearm free flap.

Restoration of oral competence must be especially addressed when considering reconstruction of the lower lip. When resection has disrupted the

central mimetic musculature or distal branches of the facial nerve, the reconstructed lip should be supported with a static or dynamic sling.[15] This is achieved with the use of the composite radial forearm–palmaris longus muscle flap. The function of the palmaris longus is to flex the wrist, which is duplicated by the flexi carpi muscle group, allowing for harvest of this tendon with little added morbidity. The folded radial forearm skin provides both external and mucosal resurfacing, whereas the tendon may be suspended to the modiolus providing support to the lip. Such a technique supplies static suspension of the lower lip improving cosmesis, but does not provide adequate oral competence during motion when used for lower lip reconstruction. To overcome these deficits, various alterations have been described. In an attempt to achieve dynamic function, Jeng et al.[16] modified the radial forearm–palmaris longus flap to include the passing of both ends of the palmaris longus tendon intramuscularly through the modiolus bilaterally. The palmaris longus is then anchored to the ends to the remaining orbicularis muscle of the upper lip near the philtral columns. This addition mimics the function of the horizontal fibers of the orbicularis oris and hence restores some integrity of an intact oral sphincter. Dynamic slings can also be incorporated into free flap reconstructions to improve the degree of voluntary control of commissure position and lip tone. Techniques incorporating both a free flap for lip resurfacing and a simultaneous temporalis sling for elevation have been described for this purpose.[17]

Further dynamic restoration is achievable with the incorporation of reinnervated muscle to replace the resected orbicularis oris, which is most commonly performed with the gracilis muscle flap.[18] This flap has been used extensively in the dynamic reconstruction of facial paralysis, and its ability to regain dynamic function after transfer is well documented. The gracilis flap is based on the adductor vessels, branches of the profunda femoris, with motor nerve input from the anterior branch of the obturator nerve. The pedicle of the caliber and length are sufficient, but often less than that of the radial forearm free flap. The lack of a skin paddle will often require free flap reconstruction for mucosal lining.

SUMMARY

Cancer of the lip is often encountered in practice. In most cases, it is easily

treated with surgical resection and reconstruction. When the cancer advanced locally, thought must be given to the reconstruction so that the rehabilitation of the patient is optimal. With all the tools available in the armamentarium of the reconstructive surgeon, good functional outcomes should be possible in the majority of cases.

In some patients with poor prognostic indicators, ancillary treatment with radiation therapy should be considered.

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13 Squamous Cell Cancer of the Oral Cavity

Laureano A. Giraldez-Rodriguez Brett Miles Eric M. Genden

EPIDEMIOLOGY

Cancer of the oral cavity represents ~30% of all cancers of the head and neck. Squamous cell carcinoma (SCC) constitutes 90% of all oral malignancies whereas the remaining 10% include cancer arising in minor salivary glands, and odontogenic cancers, and sarcomas.[1] The incidence of oral carcinoma is ~6 cancers per 100,000 in Americans with a male-to-female ratio of 2.2:1. In North America, this represents ~1.4% of all new malignancies and 0.6% of all cancer-related mortality. Based on the most recent Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute data, the overall 5-year survival for cancer of the oral cavity is 62.2% (2003 to 2009) compared to 53% two decades earlier (1975 to 1979). The average age of diagnosis is 60 years and the vast majority of patients (>95%) are older than 40 years (http://seer.cancer.gov). Although these data are important, they can be misleading because the cancer of the oral cavity encompasses diverse anatomy from the lips to the tonsillar pillars. Although the lips and the oral tongue are anatomically close, cancer in these regions of the oral cavity may behave differently. For example, carcinoma of the lip behaves very differently from carcinoma of the lateral tongue; and carcinoma of the lateral tongue behaves differently from cancers of the hard palate. The lip, the tongue, and the hard palate are anatomically included within the *oral cavity* site, yet malignancy in each of these subsites behaves very differently. This must be considered as one interprets the data because the majority of data are the results of studies inclusive of patients across the various oral cavity subsites.

ETIOLOGY

The risk factors for developing SCC of the oral cavity in North America and Europe are tobacco and alcohol consumption. Independently, they are associated with a dose-dependent risk of developing oral SCC. Cigarettes contain over 60 carcinogens.[2] Despite a decline in the rate of cigarette smoking since the release of the first US Surgeon General’s Report on Smoking and Health in 1964, 21.6% of men and 16.5% of women continue to use tobacco; ~80% of tobacco users are daily smokers.

Alcohol is another common carcinogen contributing to mucosal irritation and increased cell permeability. Excessive alcohol consumption is associated with vitamin and nutritional deficiencies, which independently contribute to oral carcinogenesis. Combined, these toxins have synergistic effects and translate to a relative risk of developing oral SCC of between 7.2 and 35.[3–5] Smokeless tobacco is associated with a twofold increased risk of oral SCC, is estimated to be used by 6% of the US adult male population, and is significantly more common in the southern United States where the rate raises to 30%.[6] In areas where chewing betel or areca nut is more commonplace, such as South Asia, this behavior is associated with a sevenfold increased risk of developing oral SCC.[7] The practice of reverse smoking, commonly practiced in India, further contributes to an increased rate of oral cavity SCC, which constitutes an impressive 25% of all cancers in that region.[8] Less well-studied risk factors include poor oral hygiene and ill-fitting dentures; however, these conditions have both been recognized as independent risk factors. The proposed etiology is that mechanical irritation produces a cascade of inflammatory mediators that contribute to the development of dysplasia and carcinoma.[9]

Over the past three decades, there has been a rise in human papillomavirus (HPV)-associated cancer of the oropharynx, oropharyngeal squamous cell carcinoma (OPSCC).[10] It is suggested that this trend may correspond with changing sexual behaviors and is consistent with the mode of transmission of HPV and the relative increased rate in males versus females.[11] The correlation between HPV and cancer of the oral cavity is less clear. Some reports demonstrate that up to 24% of oral cavity carcinomas are associated with HPV; however, most literature suggests a significantly lower association.[12,13] There remains a significant proportion of oral squamous cell

carcinoma (OSCC) that cannot be attributed to the traditional risk factors of tobacco or alcohol use, particularly among women and young patients.[5] Recent epidemiologic studies have identified an increasing incidence of SCC of the oral tongue in younger patients and found that gene-specific mutation and copy number alteration frequencies were similar between young and old patients. This observation supports the recent developments illucidating the significant role that genetic instability and genetic susceptibility play in the etiology of oral SCC and the poorly understood functional impact of smoking on carcinogenesis.[14–16]

ANATOMY

The anterior border of the oral cavity is at the junction of the skin and vermilion border of the lip.[16,17] Posteriorly, the oral cavity is limited by the junction of the hard and soft palates superiorly and the circumvallate papilla inferiorly. The anterior tonsillar pillars define the posterior lateral aspects of the oral cavity. The oral cavity is composed of the oral cavity gingiva, lip, hard palate, oral tongue, floor of the mouth, retromolar trigone, and buccal mucosa (Fig. 13.1). In addition, the underlying mandible and maxilla are often included in the anatomy of the oral cavity. The oral cavity is lined by squamous cell epithelium populated by minor salivary glands. Although minor salivary glands can be demonstrated throughout the mucosa of the oral cavity, they are most concentrated within the hard and soft palate. For this reason, minor salivary gland tumors exist most commonly within these sites in the oral cavity.

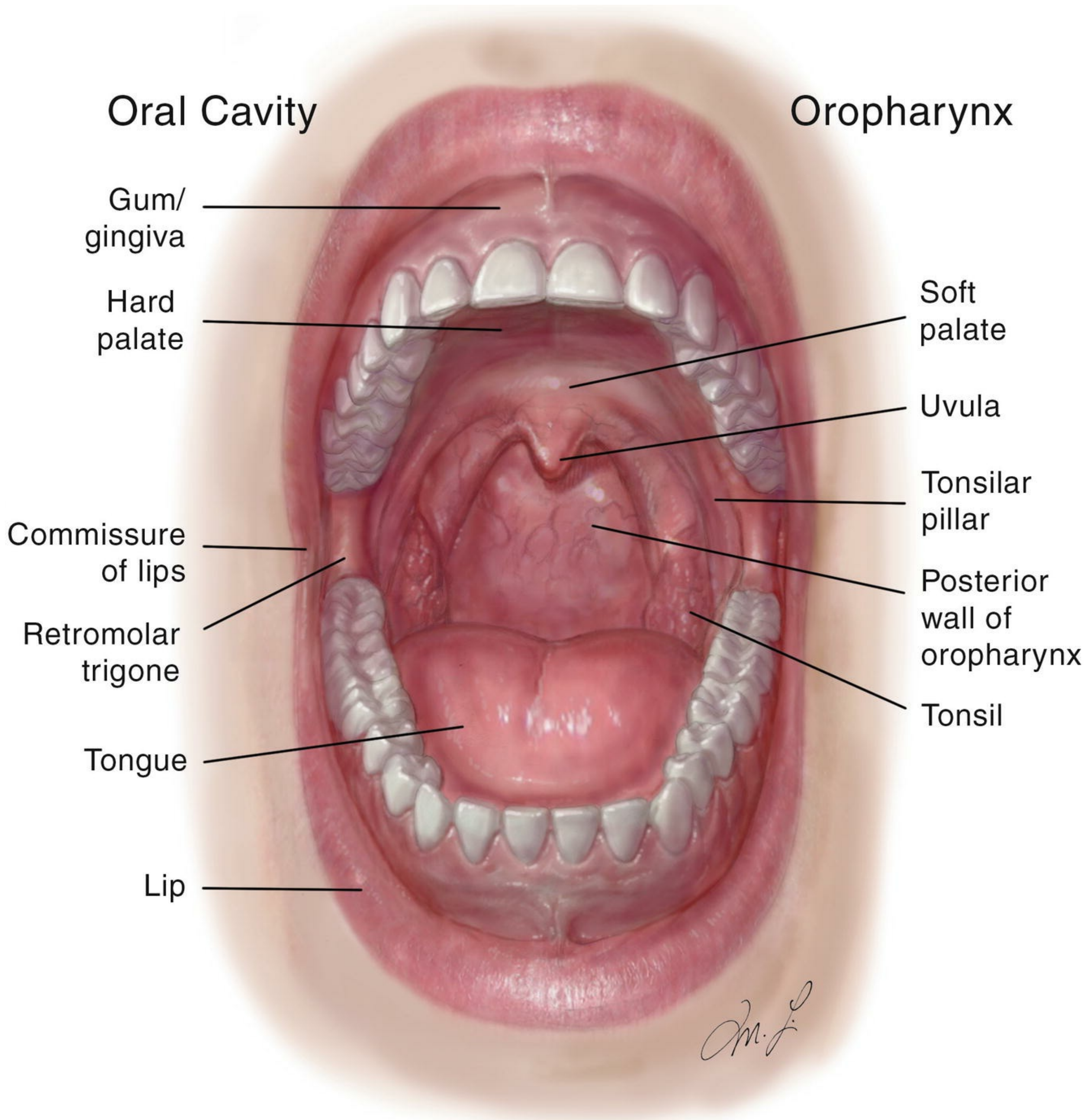


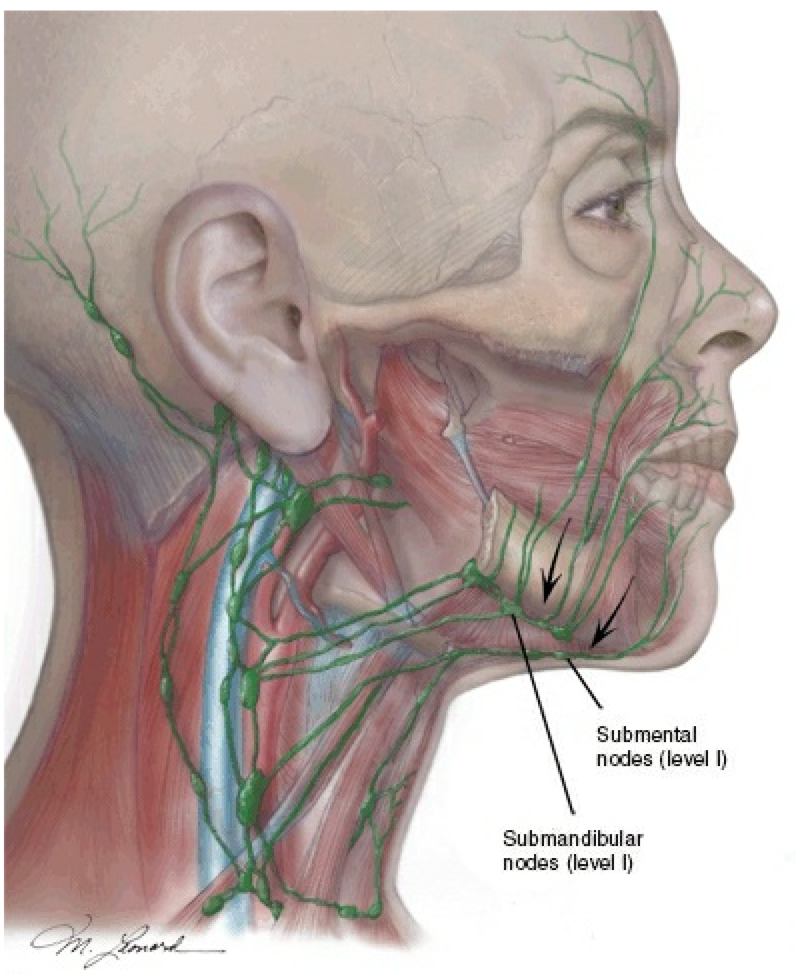
Figure 13.1. Anatomy of the oral cavity. The anterior border of the oral cavity is at the junction of the skin and vermilion border of the lip. Posteriorly, the oral cavity is limited by the junction of the hard and soft palates superiorly and the circumvallate papilla inferiorly. The anterior tonsillar pillars define the posterior lateral aspects of the oral cavity. The oral cavity is composed of the oral cavity gingiva, the lip, the hard palate, the oral tongue, the floor of the mouth, the retromolar trigone, and the buccal mucosa.

In addition, the mandibular and maxillary alveoli are included in the oral cavity. The retromolar trigone, which is an area located in the posterior oral cavity posterior to the last mandible tooth, is a common site for cancer of the oral cavity. The overlying periosteum is particularly thin in the area of the retromolar trigone, making invasion of the cortex a common occurrence. The floor of the mouth extends from the inner margin of the inferior alveolus to the ventral surface of the oral tongue. The structures of the floor of the mouth are supported by mylohyoid, geniohyoid, and genioglossus musculature. These muscles insert along the mylohyoid line found on the medial aspect of the mandible. The sublingual structures lie cranial to the mylohyoid line, whereas the submandibular structures lie below the mylohyoid line. The oral tongue located within the floor of the mouth is lined with squamous epithelium and fungiform, filiform, and circumvallate papilla. The intrinsic muscles responsible for swallowing and the articulation of speech generate the complex movement of the tongue. Several branches of the external carotid artery, including the facial and lingual arteries, provide the blood supply of the oral cavity structures.

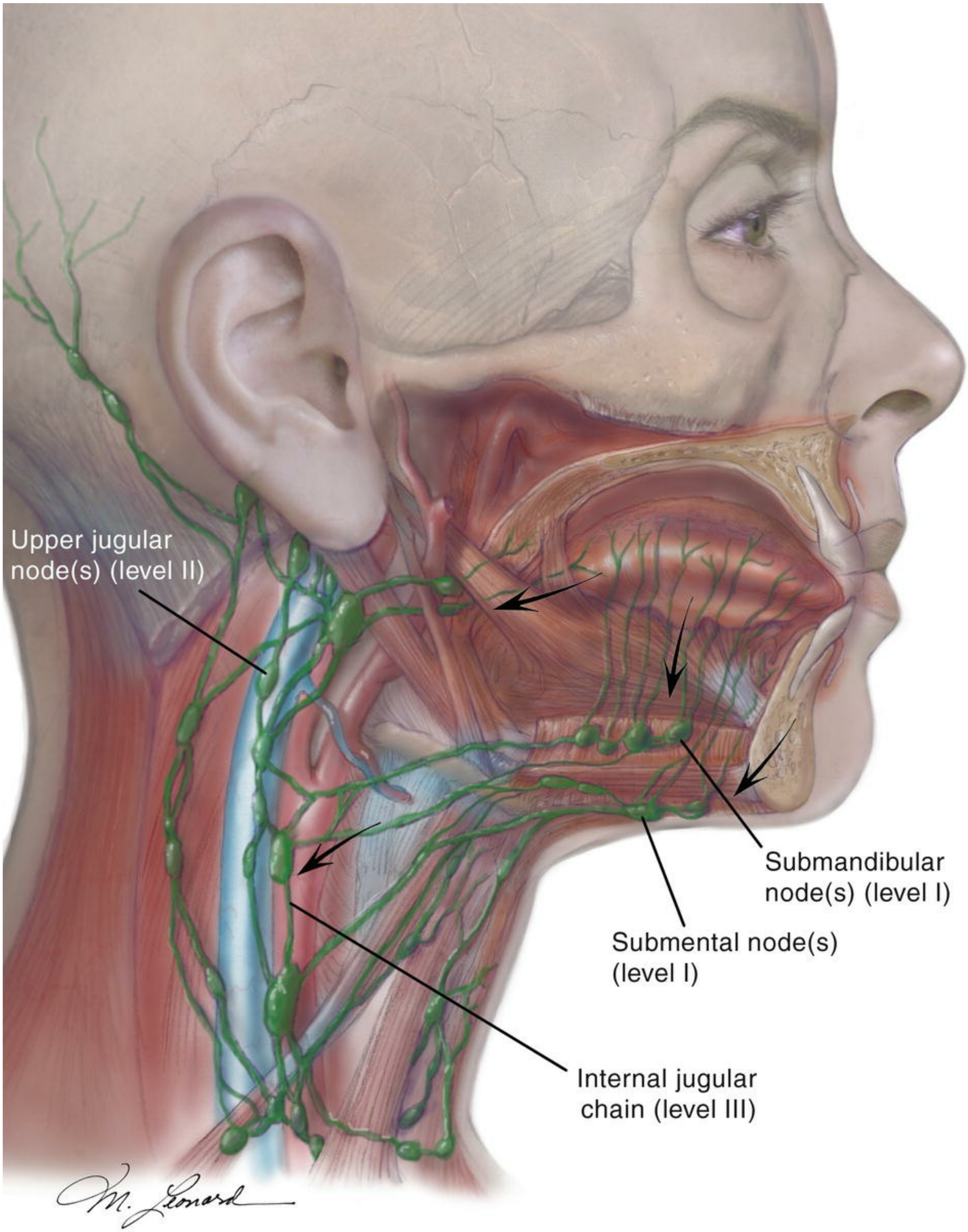
The pattern of lymphatic drainage of the oral cavity has been well established in the literature.[18–20] The presence of cervical lymph node metastasis has been repeatedly correlated with the size, depth of invasion, location, and the degree of differentiation of the primary tumor. In general, the frequency of lymph node metastasis increases with the size and depth of penetration of the lesion. Additionally, the more posteriorly a primary is located, the higher the risk of lymphatic spread to lower echelon nodal basins (level III to IV). The lymphatic spread of oral SCC generally occurs in an orderly manner, involving first levels I to II, followed by levels II to III, and finally the inferior cervical lymph nodes, level IV. However, "skip" metastases have been reported, wherein metastatic spread from oral cavity structures to lymph nodes in level IV of the neck can occur in the absence of nodal involvement in levels I, II, and III.

The pattern of lymphatic spread often follows the vascular territory of the region in which the primary cancer is located. The lip, cheek, and anterior gingiva drain to submandibular and submental lymph node basins (level I to II) and occasionally the inferior parotid nodal basin (Fig. 13.2A–C). The posterior gingiva and palate drain to the internal jugular chain and lateral retropharyngeal nodes (level II to IV). Lymphatic drainage for the tongue and

floor of the mouth includes the internal jugular, subdigastric, omohyoid, submandibular, and submental nodal basins (level I to III). The deep lymphatic network for the oral tongue consists of anterior, lateral, and central lymphatic pathways. The anterior pathway drains the tip of the oral tongue and primarily drains to level III (or less commonly level I to II). The lateral group drains the lateral one-third of the dorsum of the tongue from the tip to the circumvallate papillae to submandibular, and internal jugular nodal basins and occasionally the submental node basin (level I to III). The central pathway drains the central two-thirds of the tongue. These vessels drain to the submental region (level I) or the upper cervical chain nodal basin via the sublingual nodes (level III).[21] Primary cancers, which approach midline, often drain to bilateral nodal basins. This is especially true for cancers of the tongue and floor of the mouth as there exists significant lymphatic crossover in this region.[22,23]

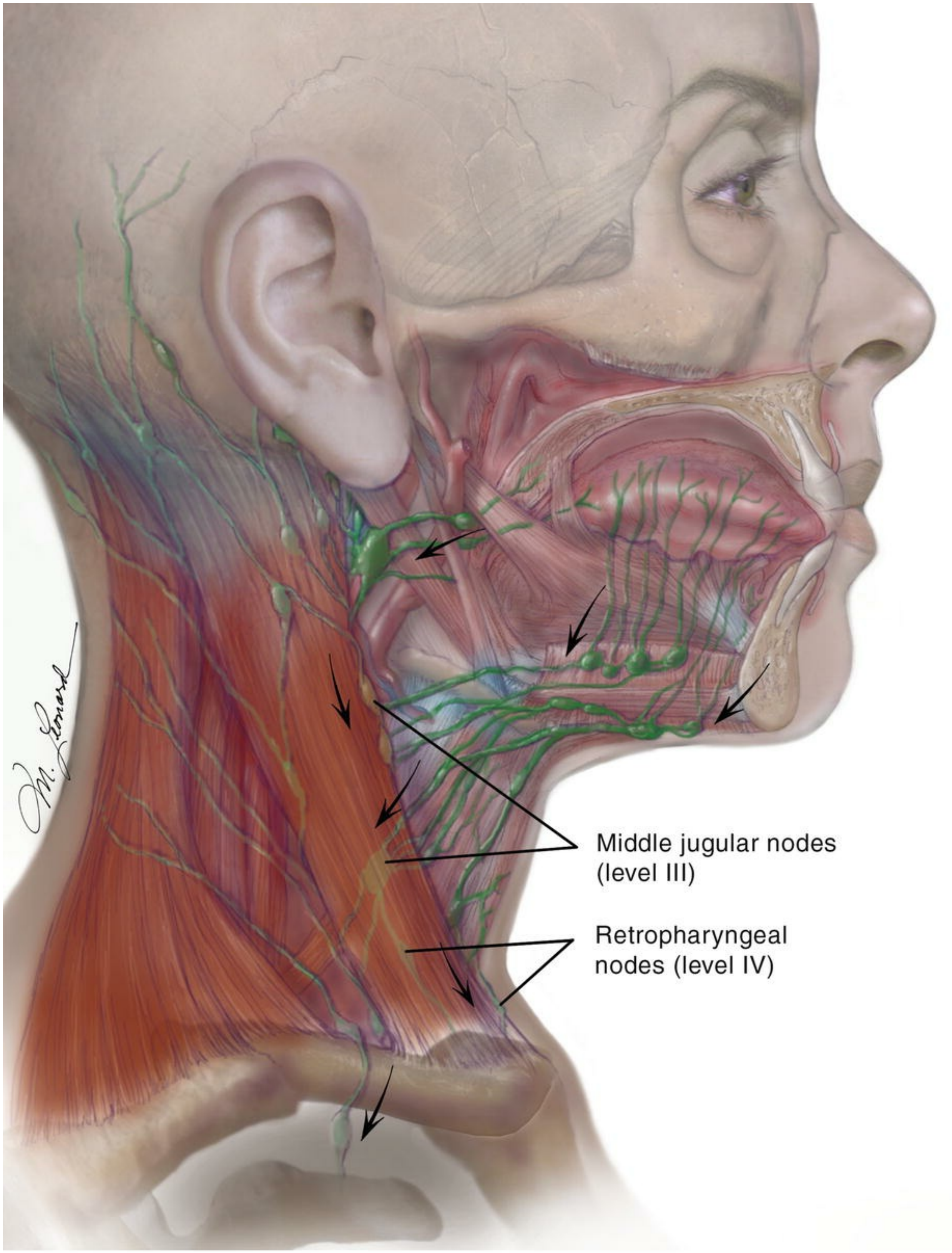


A



Upper jugular node(s) (level II)
Submandibular node(s) (level I)
Submental node(s) (level I)
Internal jugular chain (level III)
M. Leonard

B



C

Figure 13.2. A–C: The lymphatic spread of oral SCC generally occurs in an

orderly manner, involving first levels I to II, followed by levels II to III, and finally the lower cervical lymph nodes, level IV. The pattern of lymphatic spread often follows the vascular territory of the region in which the primary tumor is located. The anterior pathway drains the tip of the oral tongue and primarily drains to level III (or less commonly levels I to II). The lateral group drains the lateral one-third of the dorsum of the tongue from the tip to the circumvallate papillae to submandibular, and internal jugular nodal basins and occasionally the submental node basin (level I to III).

Premalignant Lesions of the Oral Cavity

Unlike other head and neck sites, the oral cavity can be easily examined and is therefore amenable to screening protocols to identify early cancers. Awareness of the common signs and symptoms of premalignant and malignant oral lesions is paramount to the early detection and recognition of these lesions. Pain is the presenting symptom in 50% to 60% of malignant lesions and should therefore prompt further evaluation with a biopsy, excision, or close follow-up, especially in the setting of pain that persists.[24] Patients with symptomatic lesions often present to primary care physician or dental health professional. In contrast, asymptomatic lesions can grow undetected. This underscores the importance of screening. The American Dental Association has enacted a screening program that has proven successful in identifying oral premalignancies and early cancers.

It is often difficult to differentiate premalignant lesions from early invasive cancers. Invasive SCC often develops as a result of an evolution of molecular transformations in suppressor and/or promoter genes.[24] The evolution, however, does not always follow a prescribed pathway resulting in an invasive carcinoma. Premalignant lesions of the oral cavity may be detected at any point in this progression. Some may be actively progressing toward malignancy, whereas others may remain in a state of abeyance, neither progressing nor regressing. Suspicious findings on examination include a nonhealing or indurated ulcer or a mucosal lesion with a palpable firm mass.

Leukoplakia

Leukoplakia is a descriptive term, not a pathologic diagnosis. This

descriptive terminology refers to white patches on the mucosal surface that histologically correlate with hyperkeratosis, acanthosis, and inflammatory cell changes. These changes may be premalignant or associated with atypia. Tobacco is the most commonly associated risk factor for developing leukoplakia. In a large case series of clinically diagnosed leukoplakia reviewed microscopically, only 7.6% had severe dysplasia or invasive carcinoma.[25] Over a 10-year period, leukoplakia has been reported to progress to carcinoma in 0.9% to 17% of cases.[26] Leukoplakia may also occur without a preexisting environmental exposure. In either case, the presence of leukoplakia often warrants a biopsy, with smaller lesions undergoing an excisional biopsy. Some suggest observation of a small confluent leukoplakia lesion if there is no evidence of progression, ulceration, or change in character. Some tobacco-related keratosis present as a very thin confluent white patch over the mucosal surface in direct contact with the tobacco. These lesions are less suspicious for transformation with cessation of tobacco use. They should be followed up closely with biopsy reserved for transforming lesions.

Erythroplakia

Erythroplakia, defined as a flat red patch, is a more concerning lesion than leukoplakia and is more likely associated with atypia or progression to carcinoma. The homogeneous type of oral erythroplakia has been correlated with a 51% rate of invasive carcinoma and a 40% rate of carcinoma in situ.[27] Therefore, these lesions should be promptly biopsied and appropriately managed. Erythroplakia may present as an isolated lesion or in the presence of leukoplakia. In some cases, leukoplakia may progress to erythroplakia as the lesion develops into an invasive carcinoma.

Submucosal Fibrosis

Oral submucosal fibrosis is a chronic condition with premalignant potential that predominately affects patients from Southeast Asia with a significant history of betel quid chewing. Histologically, submucosal collagen deposition and fibrotic bands characterize submucosal fibrosis. This translates clinically to thickened and keratotic bands that restrict the pliability and flexibility of the buccal mucosa. For these reasons, the buccal mucosa becomes thickened and tight and the patients develop trismus. These lesions should be closely

monitored for the development of oral cavity SCC.[28]

CLINICAL PRESENTATION OF CANCER OF THE ORAL CAVITY MALIGNANCY

The presentation of cancers of the oral cavity may vary depending upon the histology and the location. Cancers may present as an ulcerative lesion, as a raised exophytic lesion, or as an irregular mucosal mass. Not uncommonly, ulcerative lesions may present as a subtle lesion on the surface; however, on further inspection and palpation, the lesion may extend deep into the soft tissue. For this reason, palpation is a key part of the examination. Similarly, cancers of the alveolus may present as an irregular patch of mucosa adjacent to a tooth socket. Peridental cancers may present as a limited lesion on the surface of the mucosa, yet they may extend deep into the tooth socket and mandibular canal. In contrast, exophytic lesions may present as a papillomatous mass often described as “cauliflower-like” growth. Although benign lesions may present in a similar fashion, bleeding or ulceration suggests malignancy.

Cancer of the oral cavity may present as a painful lesion; however, the presentation may be variable. Because cancers in this region are exposed to saliva, contamination with commensal and pathogenic organisms commonly leads to infection and pain. In contrast, if a malignant lesion erodes into sensory nerves, that is, the lingual or alveolar nerves, the patient may present with anesthesia or hypesthesia of the lip or oral cavity. Finally, when a patient presents with complaints of trismus, invasion of the pterygoid space must be assumed until proven otherwise. Although infection and inflammation may also result in trismus, invasion of the pterygoid muscular by carcinoma defines advanced local involvement.

Prognostic Indicators

The prognosis of oral cavity cancer is predicated on a variety of factors including stage, depth of invasion, and the presence of neural and vascular invasion. Other prognosticators include the histologic findings including an infiltrating pattern, minimal lymphocytic response, and the presence of tumor

emboli. The American Joint Committee on Cancer (AJCC) tumor, node, and metastases (TNM) staging system for oral cavity (Table 13.1) accounts for some of these factors but not all of them. All patients evaluated for cancer of the head and neck should be staged according to the AJCC system because the staging system is designed to predict the patient's prognostic based on their TNM status and also to provide a uniform platform to develop treatment strategies and compare results. It does not, however, account for all of the important histologic characteristics that may portend the biologic behavior of a cancer. The location of a cancer is another predictor of behavior, and this is often overlooked. Locoregional recurrence rates are highest in the buccal mucosa (75%), followed by the sinopalatal region (50%) and the mobile tongue (27%).[29] Although all of these subsites are a part of the oral cavity, cancers in each subsite behaves differently. To account for many of the factors not included in the AJCC system, other staging systems have been proposed in order to improve accuracy, but they have failed to gain general acceptance.[30]

Table 13.1 AJCC TNM Classification: Oral Cavity SCCA

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor 2 cm or less in greatest dimension		
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension		
T3	Tumor more than 4 cm in greatest dimension		
T4	(Lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose		
T4a	(Oral cavity) Tumor invades through cortical bone, into deep (extrinsic) muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face		
T4b	Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N3	Metastasis in a lymph node more than 6 cm in greatest dimension		
Distant Metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic Stage/Prognostic Groups			
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
IVB	Any	T N3	M0
	T4b	Any N	M0
IVC	Any T	Any N	M1

Histopathology

There are a series of histopathologic features that may have significant impact on the prognosis of oral cavity carcinoma. The depth of invasion, presence of perineural invasion (PNI), and lymphocytic response are examples of histopathologic parameters that are not included in the AJCC staging system. Extracapsular spread, which is associated with a 50% reduction in survival, has a significant impact on the prognosis of a patient with cancer of the oral cavity and regional metastases.

Depth of Invasion

The depth of invasion has been shown to accurately predict the likelihood of nodal metastasis and therefore prognosis.[31,32] The depth of invasion that warrants elective lymph node dissection in the neck is controversial and has been reported to be between 3 and 5 mm.[22] The deeper the cancer invades, the more likely the presence of occult nodal metastases and local recurrence. Yuen et al.[31] reported a retrospective review of 85 glossectomy specimens and revealed that a depth of <3 mm, 3 to 9 mm, and >9 mm is associated with a 10%, 50%, and 65% rate of regional metastases, respectively. In patients with stage I or II tongue SCC with a clinically negative neck, a depth of invasion of >4 mm has been associated with a risk ratio of 9.4 in developing cervical metastases within a 5-year period.[32] Ganly et al. retrospectively reviewed a cohort of 164 early-stage oral tongue SCC in which multivariate analysis indicated that cancer thickness <4 mm versus ≥ 4 mm independently and significantly predicted regional recurrence-free survival of 94% versus 72%, respectively.[33] As a result of this study and others, 4 mm has emerged as the more commonly accepted depth of invasion mandating management of the neck. However, most of these studies are retrospective. The ability to detect occult micrometastases in cervical lymph nodes is dependent on the number of histologic sections prepared from each lymph node and may be missed during routine histopathologic evaluation.[34] Therefore, the data related to this topic are only as reliable as the methods used to assess the lymph nodes.

Perineural Invasion and Lymphovascular Invasion

PNI and lymphovascular invasion (LVI) are poor prognostic features also not

included in the TNM staging.[29,35] As a result, these features influence the need for adjuvant therapy. The presence of PNI or LVI has independently been associated with a compromise in disease-free survival; however, the addition of postoperative radiation therapy has been shown to improve survival.[36]

Extracapsular Spaced and Positive Margins

The presence of extracapsular space (ECS) of pathologic lymph nodes is the most significant prognostic feature and has been associated with a 50% reduction in overall survival. Despite adjuvant therapy, up to one-third of patients with ECS will experience either locoregional or distant recurrence.[37,38] Similarly, positive margins after surgical excision that cannot be re-resected in a timely manner are associated with a poor prognosis. A comparative analysis of the selection criteria, clinical and pathologic risk factors, and treatment outcomes of two randomized control trials (the EORTC[39,40] and RTOG trials[40]) was performed to determine the indications for postoperative concurrent chemoradiation therapy that would offer a survival advantage. This study determined that microscopically involved resection margins and extracapsular spread of cancer from neck nodes are the most significant prognostic factors for poor outcome. Furthermore, this study demonstrated that concurrent chemoradiotherapy offered a significant survival advantage for advanced cancer of the head and neck in the setting of ECS or microscopically positive involved surgical margins.[41] Although ECS is a nonmodifiable risk factor, the presence of positive margins can potentially be avoided, and therefore, when possible, it is critical to achieve a negative surgical margin.

Mandibular Invasion

Plain radiography has been used extensively in the past for the diagnosis of extensive cancer invasion of the mandible; however, subtle changes associated with the cortex have been more difficult to identify. The introduction of the panoramic x-ray, computed tomography (CT), and magnetic resonance imaging (MRI) scans has increased the accuracy of preoperative imaging and staging. Significant debate still exists regarding the optimal modality or combination of modalities recommended for preoperative assessment. Although CT is a very accurate method for

identifying gross bone invasion,[42] prior work has suggested that bone invasion may be missed in as many as 27% of patients with preoperative CT scans (Fig. 13.3). The sensitivity of CT scan for bone involvement of the retromolar trigone is ~50% with a negative predictive value of 60%; however, the positive predictive value is ~90%. It has been concluded that although the CT scan is accurate when bone erosion is clearly identified, its negative predictive value is unacceptably low and therefore an inaccurate indicator of bone invasion at the retromolar trigone. The CT scan renders an excellent view of both the soft tissue and bone of the mandible; however, it has several limitations, the most significant being artifacts caused by dental amalgams. Dental amalgams commonly create a shadow leading to artifact that can obscure invasion of the mandibular cortex. Additionally, the CT scan may misleadingly detect defects in the cortex secondary to irregular tooth sockets or periapical disease.

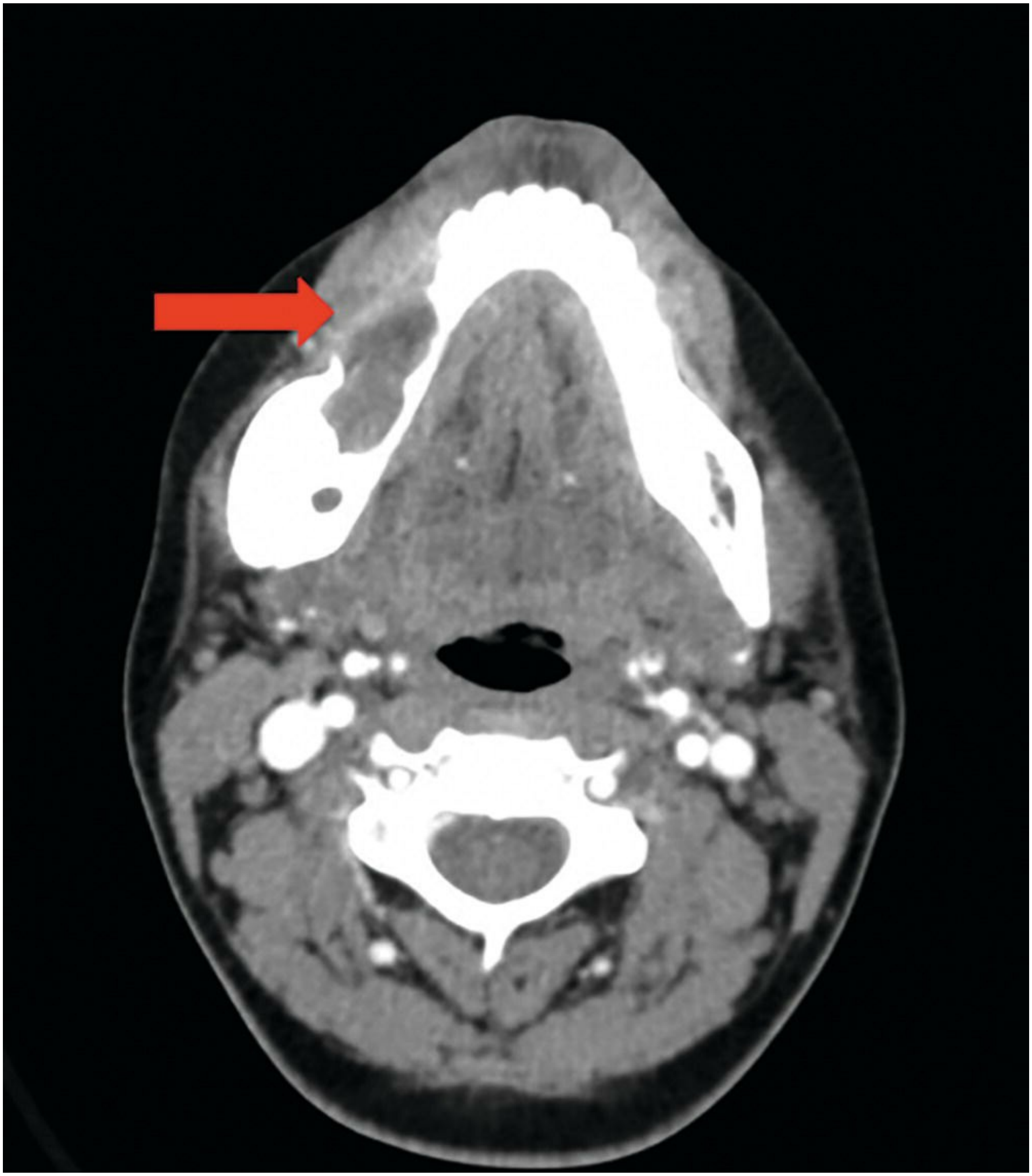


Figure 13.3. The tumor may involve the mandible by adherence or direct extension into the cortex or more deeply involve the mandible by infiltration into the medullary space. In general, osseous invasion is evaluated with CT imaging. (*Arrow* marks mandibular invasion.)

In light of these shortcomings, several investigators have reported on the

use of a DentaScan. The DentaScan was introduced in the early 1980s to assist oral maxillofacial surgeons in planning for osseointegrated implants. The DentaScan images are derived by reformatting standard axial CT scans in two views, panelliptical and parasagittal. This reformatting permits assessment of the buccal and lingual cortices. The diagnostic value of the DentaScan is accurate yielding a sensitivity of 95% and a specificity of 79% with a positive predictive value of 87% and a negative predictive value of 92%. The DentaScan is an accurate method for preoperative evaluation of invasion of the mandible in patients with SCC of the oral cavity.

Whereas the CT scan and DentaScan may offer excellent methods for assessing bone, the MRI scan offers the advantage of imaging soft tissue and potentially the medullary cavity space. Several studies have examined the use of MRI in assessing invasion of the mandible and it has been concluded that the MRI scan is superior for evaluating the medullary space of the mandible[43] but inadequate for assessing mandibular invasion. Shaha[44] examined the value of various studies including panoramic x-rays, dental films, routine mandible films, bone scans, CT scans, and MRI and found that CT scanning was not very helpful mainly because of the presence of irregular dental sockets and artifacts. Many suggest that clinical evaluation is the most accurate in determining the presence of bone invasion and the optimal method of resection, marginal versus segmental.

Most centers consider the combination of a CT scan and a panoramic x-ray acceptable for preoperative imaging of the mandible and maxilla; however, the most accurate measure of bone invasion is determined clinically. Unless there is frank invasion of the cortex, periosteal stripping followed by frozen section examination at the time of surgery is often the most reliable way of detecting bone invasion.

Traditionally, invasion of the mandible by oral SCC has been considered a poor prognostic indicator and has remained one of the criteria defining a T4 stage. However, there are conflicting reports as to the prognostic significance of bone invasion. Recently, a multivariate analysis of nearly 500 patients with oral SCC revealed that there was no association between cortical invasion and overall or disease-specific survival. However, medullary invasion independently predicted a reduced overall and disease-specific survival.[45]

DIAGNOSIS AND EVALUATION

The initial evaluation of a patient with an oral cavity lesion consists of a detailed history including the patient's oral hygiene practices as well as use of alcohol and tobacco. The oral cavity is easily amenable to examination, and this should be performed thoroughly by inspection and palpation of all the oral cavity subsites. Although brush biopsies can be easily performed and are noninvasive, their sensitivity and specificity are low.[46] Suspicious changes in the mucosa should be evaluated with a full-thickness surgical biopsy to include the pathologic architecture required to diagnose invasive carcinoma. Following an oral cavity examination, one should perform a detailed examination of the neck. Either direct or indirect examination of the upper aerodigestive tract should be part of the clinical examination especially in a patient at high risk for cancer of the head and neck. The presence of second primaries of the upper aerodigestive tract is common and should be evaluated by physical examination and with dedicated radiography.[47] Distant metastases should be ruled out, especially with advanced oral malignancies, using dedicated imaging. PET-CT, discussed below, has emerged as an optimal choice in investigating metastatic cancer.[48] However, chest radiographs and CT scanning of the chest are also useful screening modalities, especially in those patients with a lower locoregional disease burden.

Local Cancer

Following a diagnosis of SCC, a thorough assessment of the extent of the cancer and the potentially premalignant surrounding mucosa is required. Fluorescence imaging has proven a useful tool in increasing the sensitivity of identifying pathologic mucosa and is a promising technology.[49] Although extensive lesions may present with neuropathies, trismus, and decreased tongue mobility, the absence of these symptoms does not rule out invasion. CT with intravenous contrast evaluates the extent of mucosal, soft tissue, and bone involvement. MRI offers superior accuracy in predicting the degree of soft tissue or neural involvement and can be helpful in determining bone marrow invasion especially when CT is compromised by dental artifact. Enhancement of named nerves such as the lingual, hypoglossal, or alveolar nerve on MRI may predict PNI and is especially helpful in nonepidermoid

carcinomas such as adenoid cystic carcinoma. However, CT and MRI have equivalent accuracy for staging the oral cavity primaries and both are limited in characterizing superficial lesions.[50]

Invasion of the Mandible

The presence and extent of invasion of the mandible portend a worse prognosis and determine the extent of surgical resection.[45] The cancer may involve the mandible by adherence or direct extension into the cortex or more deeply involve the mandible by infiltration into the medullary space. In general, osseous invasion is evaluated with CT imaging (Fig. 13.3). Alternative techniques may be useful including dental radiographs, panoramic radiographs, cone-beam CT scanning, MRI, and bone scintigraphy with single photon emission computed tomography (SPECT). CT provides adequate assessment of the soft tissue and bony architecture; it is however limited by dental artifact and irregularly shaped alveoli or periapical disease that may incorrectly be attributed to mandibular invasion. MRI offers superior assessment of the soft tissue and medullary space but is inferior in determining cortical involvement and is limited by motion artifact. Compared to MRI and SPECT imaging, which overestimate bone invasion, CT tends to underestimate cortical invasion.[51,52] For example, the negative and positive predictive values of CT in predicting bony involvement of the retromolar trigone are 60% and 90%, respectively.[42] The DentaScan protocol, derived by reformatting standard axial CT scan in two views, affords assessment of the buccal and lingual cortices with a negative and positive predictive value of 87% and 92%, respectively, in predicting mandibular invasion.[53] MRI is superior for evaluating the medullary space of the mandible but not in determining cortical involvement alone.[43] Other modalities with a high diagnostic accuracy of cortical involvement include the technetium 99 m bone scintigraphy.[54]

Although clinical evaluation and imaging are critical in predicting the presence of bony invasion and the extent of surgical resection in the absence of gross invasion, intraoperative periosteal stripping followed by frozen section analysis is likely the most reliable indicator of bone invasion.[37]

Cervical Lymphadenopathy

To evaluate the presence and extent of lymphadenopathy in the neck, both CT and MRI are routinely used and have been shown to be equivalent.[55,56] Generally speaking, in the occult neck, between 40% and 60% are identified on CT or MRI[37] (Fig. 13.4). Several advances in MRI technology, diffusion-weighted imaging and dynamic contrast enhancement, have been applied with improved diagnostic accuracy.[57,58] In addition, the introduction of ultrasmall superparamagnetic contrast agents that preferentially accumulate in benign compared to malignant lymph nodes may further improve accuracy.[59] However, this is limited by requiring delayed images 24 to 48 hours after contrast administration.

Figure 13.4. To evaluate the presence and extent of lymphadenopathy in the neck, cross-sectional imaging tests including CT are routinely used with excellent accuracy. (*Arrow* marks regional lymph node metastasis.)

Ultrasound is also commonly used to evaluate the neck, and although the accuracy of this technique depends on the experience of the sonographer, it has the unique advantage of being combined with a fine needle aspiration (FNA) with a 100% specificity. In the clinically negative neck, ultrasound-

guided FNA detects occult disease with a sensitivity of up to 48% to 73% that is comparable to CT and MRI.[55,60]

Positron emission tomography (PET) is a functional imaging technique utilizing a radiolabeled tracer, namely, 18-fluoro-2-deoxyglucose (FDG), which allows for the in vivo localization of increased tissue metabolism. FDG is a glucose analog and has preferential uptake in tissues with increased metabolism as is often the case in malignancies. As the radiolabeled FDG is transported intracellularly, it is phosphorylated by hexokinase, preventing any further metabolism, and in turn collides with gamma rays in an annihilation reaction that produce positrons that are measured by the PET scanner. PET has been fused with a noncontrast low-dose CT (PET-CT) and MRI (PET-MRI), which have significantly improve on the lack of anatomical detail with PET alone.[61] However, this has not translated to an improved diagnostic accuracy compared to PET alone.[48] It is important to note that the specificity of PET is limited by variable physiologic uptake and its sensitivity is significantly decreased with lesions <5 mm in size.[62] Therefore, the reported sensitivity of PET-CT for detecting lymph node metastases is similar to that of CT or MRI alone.[63] The primary role of PET in oral SCC is in detecting subclinical metastatic disease and in posttreatment follow-up.

Molecular Markers

There are several tumor markers that have been associated with a poor prognosis in oral SCC. Although there is potential that in the future, these markers will identify patients with aggressive disease and dictate the choice of adjuvant therapy, the prognostic relevance of most tumor markers is still not quite clear.[64–66]

MANAGEMENT OF CANCER OF THE ORAL CAVITY

The overwhelming majority of cancers involving the oral cavity are SCC; however, minor salivary gland cancers may also occur. Epidermoid cancer of the oral cavity may be treated with radiation, surgery, or combined therapy. Although the goal is to achieve a cure, it is optimal to manage patients with the fewest modalities possible, as each modality is associated with less

treatment-related morbidity and thus contributes to a decrement in quality of life.

Early Stage

Stage I and II oral SCC can be treated with equivalent oncologic outcomes with either radiation therapy or surgical resection. Therefore, the optimal choice is dictated by a combination of the expected quality of life, patient preference, and comorbidities. However, as compared to cancer arising in other sites in the upper aerodigestive tract, the oral cavity is more often treated with surgery as the primary modality. Most early-stage oral SCC can be effectively managed surgically through a transoral approach with minimal morbidity during a single intervention. Although radiotherapy has equivalent oncologic outcomes, the potential for long-term radiation sequelae, such as xerostomia, taste disturbance, fibrosis, and osteoradionecrosis, contributes to surgical management being the mainstay of therapy. Furthermore, radiation therapy requires daily treatments for 6 to 7 weeks.

Advanced Stage

Stage III and IV cancers require a multimodality approach that most often consists of surgery followed by postoperative radiation or chemoradiation therapy. Preoperative radiation or chemoradiation therapy has been applied in the treatment of advanced oral SCC with success.[67] However, this technique may be associated with an increased risk of postoperative complications. Furthermore, although the original cancer may decrease in size and improve the ability to surgically ablate the remaining cancer, it is common to surgically address the original border of the cancer to remove potentially viable islands of cancer cells.[37] Traditionally, T4 lesions with bone invasion have had superior outcomes with primary surgery followed by postoperative therapy; however, more recently, there is evidence that primary chemoradiotherapy for selected T4 lesions may have comparable oncologic and functional outcomes.[68]

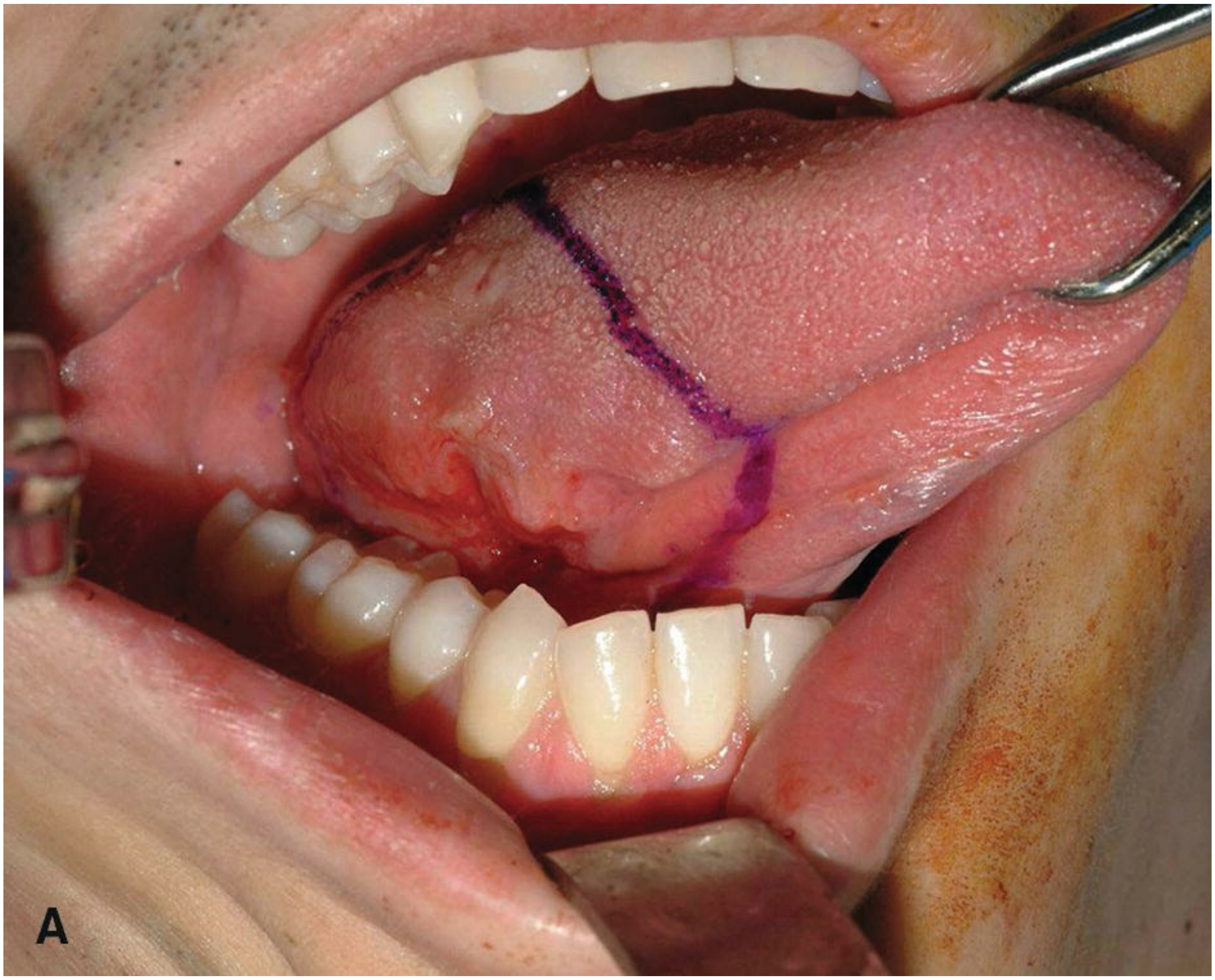
The primary oncologic goal of surgical resection of the primary cancer is to achieve a negative margin. Close margins are generally considered <5 mm. In the setting of a positive margin, surgical re-resection is recommended provided the original margin can be identified and that re-resection will not

significantly compromise functional outcomes. Radiation therapy to the primary is indicated in cases with close margins, lymphovascular or PN invasion, T3 or T4 cancer, or high-grade lesions. The indications for postoperative radiation therapy to the neck include N2 or N3 disease.[69] The indications for the addition of chemotherapy to postoperative radiation in oral SCC are positive margins or extracapsular extension, with many also including multiple pathologic lymph node involvements as an indicator.[40,41]

Cancer of the Oral Tongue

The oral tongue is the most common location for oral SCC. Early-stage cancer can be routinely excised via a transoral approach. Care should be taken to provide a 1-cm circumferential mucosal and deep margin. Frozen section analysis can aid in determining negative margins. It is important to recognize that achieving negative deep margins within the musculature of the tongue can be challenging to achieve when the initial deep margins are positive. This is due to the elastic recoil of transected muscle fibers, which can transport cancer cells deeper within the tongue musculature. Therefore, it is recommended to consider initially taking wide margins around cancers infiltrating into the tongue musculature.

The partial glossectomy defect may be closed primarily or left to granulate secondarily, or a split-thickness skin graft or acellular dermal graft can be applied to prevent tethering, particularly when the floor of the mouth is involved. For more advanced OSCC that results in an ablative defect greater than one-third of the tongue (Fig. 13.5A), one should consider a vascularized free tissue transfer to improve speech and swallow and help prevent an orocutaneous fistula (Fig. 13.5C). Adjacent submandibular or sublingual ducts should be recognized and rerouting or marsupialization should be considered if appropriate. Cancers that extend to involve a significant portion of the base of the tongue, floor of the mouth, or lingual surface of the mandible should prompt the surgeon to consider alternate approaches including a transcervical approach or a paramedian or posterior mandibular osteotomy, which facilitates obtaining free margins in all three dimensions. The factors influencing the need for, and extent of, an elective neck dissection are controversial and are discussed below. Lymphadenopathy that is clinically or radiographically suspicious for pathologic involvement should be addressed with a neck dissection.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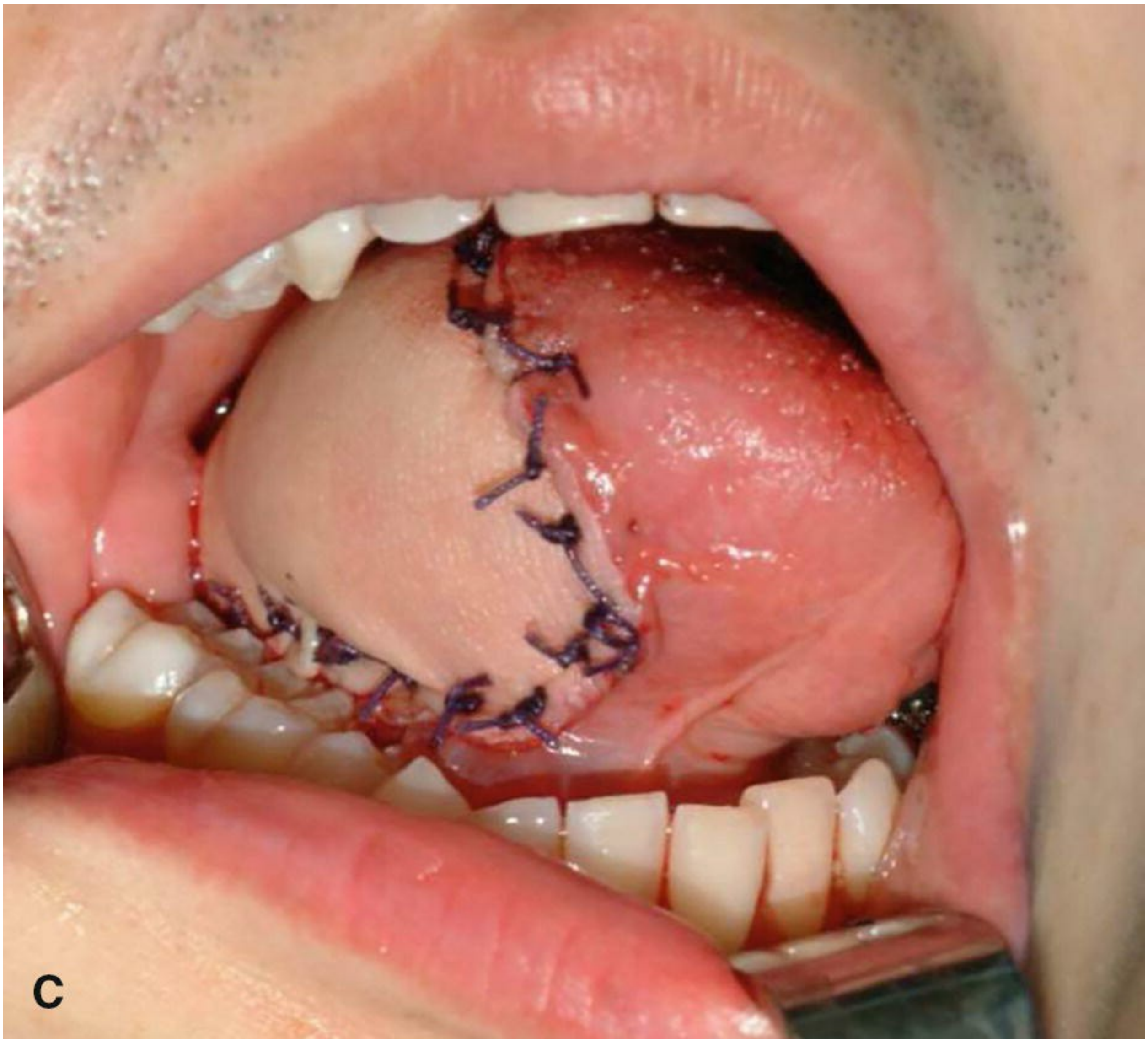

Figure 13.5. A–C: For more advanced oral cavity squamous cell cancer that results in an ablative defect greater than a third of the native tongue, one should consider a vascularized free tissue transfer to improve speech and swallow and help prevent an orocutaneous fistula. This group of photos demonstrates the radial forearm donor site used to reconstruct the oral tongue defect.

Floor of the Mouth

The floor of the mouth is rich in neurovascular structures including the lingual artery and nerve, the hypoglossal nerve, as well as the submandibular duct and sublingual gland. This area lacks a fascial boundary, and therefore, cancers in this region have the ability to invade deeper structures and lymph

node metastases are common. Clinical signs and symptoms provide valuable information as to the involvement of the lingual or hypoglossal nerve or submandibular duct. MRI is a valuable tool in determining the extent of soft tissue and PN invasion and is less affected by dental artifact compared to CT. The role of elective neck dissection is controversial with some suggesting that clinically negative neck can be observed for regional metastases because subsequent pathologic adenopathy can be effectively addressed with surgery and radiotherapy without impacting on survival.[70] Others have recommended elective neck dissection for early removal of occult disease with minimal morbidity.[71,72]

Most cancers of the floor of the mouth can be adequately excised through via a transoral approach or combined with a transcervical approach. For advanced cancers, a mandibulectomy may be required to provide for an adequate surgical margin and can readily be performed without a lip-splitting procedure. As always, a wide excision of the primary cancer, including at least a 1-cm margin of normal tissue, should be performed. Care should be taken to address the ipsilateral lingual artery, with careful attention to the location of the hypoglossal nerve. Although branches of the hypoglossal nerve are inevitably sacrificed during the ablation, the remaining trunk should be preserved to provide motor innervation to the remaining tongue. Unless dictated by the oncologic resection, excision of the sublingual gland is associated with increased complication rates and should not be performed routinely.[73] Should an osteotomy be expected, the preoperative assessment should include reviewing the available images (CT or panorex) to examine the location of the proposed osteotomy with careful attention to the adjacent teeth and mental foramina.[74]

Mandibular Invasion

The degree of invasion of the mandible will dictate the extent of surgical resection and may include either a marginal mandibulectomy or a segmental mandibulectomy. Cancers that are confined to the periosteum or outer cortex without medullary bone involvement may be managed with a marginal mandibulectomy provided that there remains at least 1 cm of native mandible (Fig. 13.6). Cancers extending to involve the medullary bone can travel within the neurovascular bundle both proximally and distally and should be managed with a segmental mandibulectomy. The extent of the

mandibulectomy is complicated by the inability to obtain bony frozen sections. While the use of preoperative imaging may predict bone erosion, intraoperative clinical evaluation with periosteal stripping increases the sensitivity of bone erosion and helps determine the extent of surgery.[29]

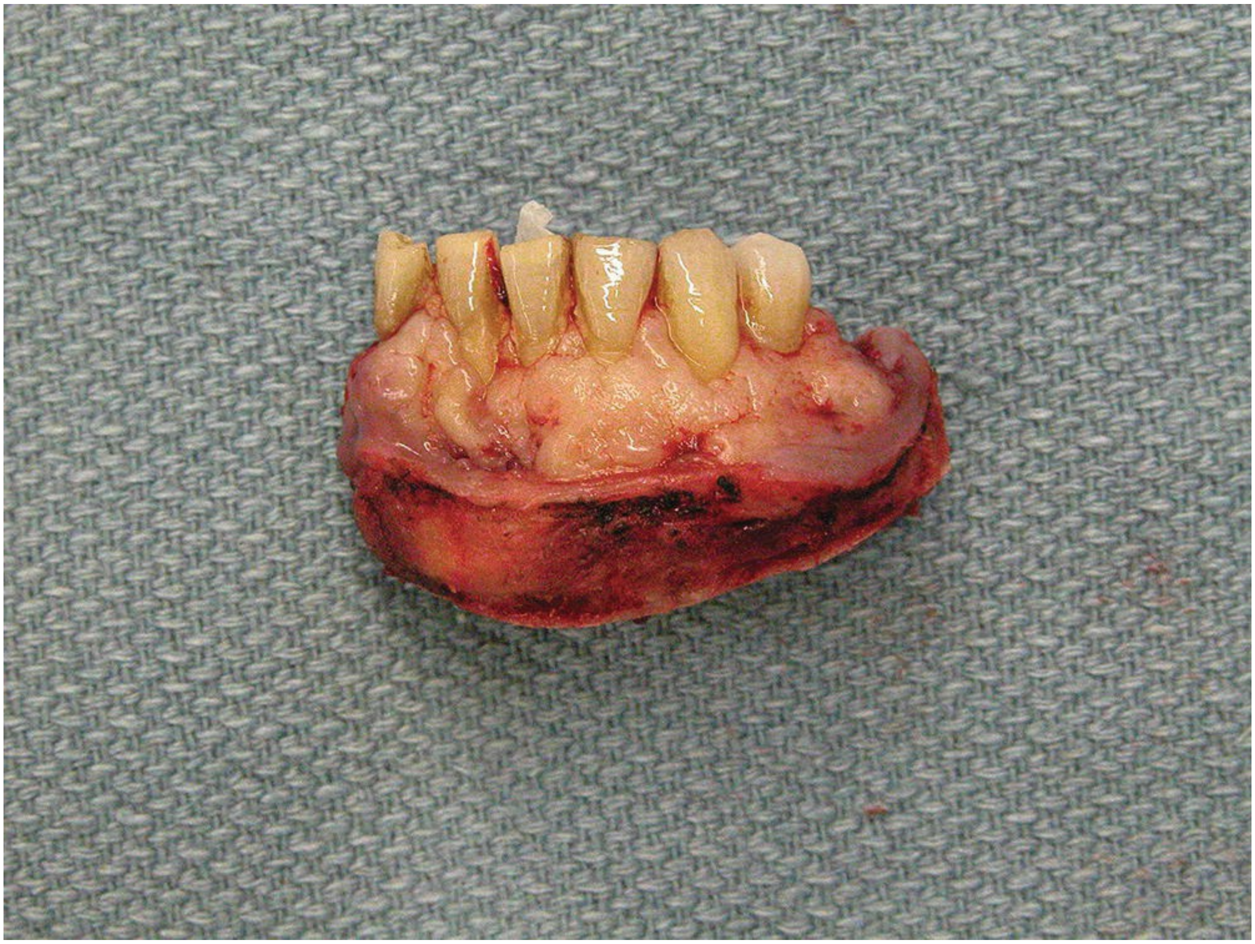

Figure 13.6. Cancers that are confined to the periosteum or outer cortex without medullary bone involvement may be managed with a marginal mandibulectomy provided that there remains at least 1 cm of native mandible. This photo demonstrates the marginal mandibulectomy specimen.

The periosteum presents a barrier to cancer spread. However, long-standing or histologically aggressive cancers can erode the periosteum and invade the adjacent mandible. Specifically, this process can be *infiltrative* or *erosive* in nature. The *infiltrative* process invades the cancellous bone through finger-like projections without the intervening connective tissue layer and has minimal osteoclastic activity. The *erosive* process is

represented by a broad front that includes the connective tissue layer and has an aggressive osteoclastic behavior. These distinct behaviors have an impact on disease-free survival, with the infiltrative pattern portending worse outcomes.[75] Although in most centers invasion of the mandible is an absolute indicator for postoperative radiation therapy, others have suggested that superficial invasion without other poor pathologic indicators can be managed conservatively. Nonetheless, the infiltrative pattern is a poor prognostic indicator and we feel that such cases should be managed with postoperative radiation therapy.[37]

Oral cavity cancer can extend along the mucosa to involve the attached gingiva where it comes in close contact with periosteum. At this point, the cancer cells will continue along the path of least resistance. In dentate patients, this will often occur as the cells migrate down the alveolus in the medullary bone. In edentulous patients, this path may proceed through defects with cortical bone at the site of prior dentition and can lead to unimpeded access to the medullary bone of the mandible. Less commonly, cancers will gain access to the mandible via the mental or mandibular canals.

Retromolar Trigone

Cancer involving the retromolar trigone has been associated with a relatively lower 5-year survival and an increase in locoregional recurrence relative to other oral cavity subsites. This may be related to an underappreciated rate of bone involvement based on imaging criteria. Therefore, a higher suspicion of bone involvement should be considered in primaries along the retromolar trigone, and at least a marginal mandibulectomy should be considered to obtain clear margins.[42,76]

Buccal Mucosa

Cancer of the buccal mucosa constitutes fewer than 10% of oral cavity SCCs. The disease can occur in one of two forms: verrucous carcinoma an indolent form of the disease and invasive SCC, the more aggressive form of the disease. Verrucous carcinoma is a progressive lesion with high recurrence and excellent 5-year survival rates. It has a low incidence of bone invasion and cervical node metastasis is unusual. The disease often derives from the benign precursor, proliferative verrucous hyperplasia. Surgery is the preferred

treatment. In contrast, invasive SCC is associated with a relatively poor 5-year survival and an increase in locoregional recurrence.[77] The primary therapy consists of a wide surgical excision and it is essential to achieve negative margins. More than one-half of buccal mucosa present as deeply invasive tumors, and MRI is an ideal imaging modality to characterize the extent of the cancers and involvement of soft tissue within the masticator space.[58] The proximity of the cancer to the parotid duct and potential tracking along the duct should be considered. When the duct is in close proximity, a frozen section margin from the duct can be very useful, and often repositioning of the parotid duct is required. Invasive cancers that involve the buccal adipose tissue should be treated by resecting the entire adipose tissue pad. Involvement of the masseter muscle and hard palate should also be ruled out.

The buccal mucosa is associated with a rich lymphatic network, and therefore, the presence of pathologic adenopathy should be carefully evaluated. Ipsilateral neck dissection is indicated for > T1 lesion and is often considered for T1 lesions suspicious for deeper invasion or with >5 mm thickness.[78,79] Careful attention to the perifacial lymph nodes is paramount to clearing pathologic adenopathy as these are often the first echelon nodes from a buccal mucosa primary. The addition of postoperative radiation therapy is reserved for cancers involving the buccinator muscles or associated with pathologic adenopathy or with poor prognostic indicators mentioned previously.

Hard Palate

In contrast to other subsites where SCC is the most common malignancy, the hard palate consists of abundant minor salivary glands and therefore is the site of both benign and malignant salivary gland cancers. Superficial or benign salivary gland cancers can be managed with simple excision using the periosteum of the hard palate as the deep margin. However, salivary gland cancers, similar to SCC, require wide local excision, often requiring removal of the hard palate, alveolus, or even dentition to achieve negative margins. Preoperative imaging is critical to determine the extent of cancer involvement and particularly bone invasion. High-resolution CT is a superior tool for characterizing the palatal and nasal bones. Cancers in or near the greater palatine foramen or the trigeminal nerve should be investigated for neural

involvement. Clinically, this may present as pain or anesthesia in the nerve distribution. MRI with gadolinium can be used to determine nerve invasion as evidenced by nerve edema or enhancement. Neurotropic salivary cancers of the palate, including adenoid cystic carcinoma, may have quite extensive proximal perineural spread to the pterygomaxillary space, foramen rotundum, and even the cavernous sinus, requiring appropriate preoperative imaging for staging and treatment planning.

Cervical metastases from minor salivary gland cancers of the hard palate are uncommon, and therefore, neck dissections should be reserved for clinically or radiologically suspicious lymphadenopathy.

NECK

The neck may be treated electively with surgery or irradiation. The clinical indicator for an elective neck dissection in OSCC is a topic of ongoing debate. The reported incidence of occult cervical metastases varies from 6% to 46% and is a reflection of the dependency of identifying occult metastases on the choice of imaging modality for preoperative assessment of nodal metastases and the technique and thoroughness in identifying involved lymph nodes on pathology. The classical works of lymph node metastases performed by Lindberg et al.,[80] were carried out prior to the widespread application of CT. Since then, there is still no single preoperative imaging modality that can reliably detect nodal micrometastases. The diagnostic accuracy of CT and MRI is limited among N0 oral cavity SCC patients.[81–83] Despite the reasonably high overall accuracy of PET-CT in the N0 neck, there is limited sensitivity for small metastatic deposits and this is further confounded by a relatively high number of false-positive findings.[82] Furthermore, immunohistochemistry and molecular analysis of pathologic neck specimens can identify occult metastases that can be missed on traditional light microscopy.[84,85] Therefore, for T1 stage cancer with a clinically N0 neck, a combination of the cancer's location, grade, and tumor depth can help guide the decision to perform an elective neck dissection. The use of a selective supraomohyoid neck dissection of levels I to III as the elective treatment of the neck is well established, with some authors extending the dissection to involve level IV to address "skip metastases".[86,87] Several recent prospective trials have demonstrated that level IIB rarely is

involved with isolated cervical metastases, and therefore, the added morbidity to the accessory nerve can be reliably spared in most elective neck dissections of oral cavity cancers.[88,89]

Traditionally, patients with clinically palpable metastatic lymph nodes were treated with a radical neck dissection of levels I to V lymph nodes of the neck including sacrifice of the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve. Ward et al. modified this technique to spare the spinal accessory nerve,[90] and subsequent modifications included sparing of the internal jugular vein and the sternocleidomastoid muscle commonly known as the modified radical neck dissection. The risk of level V cervical lymph node metastasis in oral cavity SCC is low, and therefore, the utility of a level V dissection, unless clinically or radiographically apparent, is low for most of these lesions.[91,92] Recently, several investigators have reported employing a selective neck dissection, including levels I, II, and III with similar locoregional controls and overall survival compared to the modified radical neck dissection.[93,94] Selective neck dissection can be used to effectively treat clinically positive metastases to the neck in selected patients, particularly when adjuvant radiotherapy or chemoradiotherapy is also included in the overall treatment scheme.[14,94] However, others recommend a more aggressive cervical neck dissection with advanced-stage disease.[95,96] Bilateral neck dissection should be performed in the elective setting for cancers involving or approaching midline structures and should be considered in patients with ipsilateral metastases.[97] As discussed earlier, the use of postoperative irradiation often with chemotherapy to the neck is reserved for large or multiple metastatic lymph nodes, metastatic nodes in level IV or V, or extracapsular extension.[39,40]

SENTINEL NODE BIOPSY

Sentinel lymph node biopsy (SLNB) has been successfully applied as a minimally invasive technique to determine the presence of metastatic cancer in cutaneous melanoma and breast cancers. It has also recently been applied in the management of oral and oropharyngeal SCCs. Although it has become part of standard practice in many regions of the world, it is considered to be still under extensive investigation in North America. The variable lymphatic drainage and the presence of deep lymphatics in the oral cavity and neck as

well as the proximity of the primary site to draining nodal basins make routine application of this method difficult. Nonetheless, SNLB has potential in decreasing the number of elective neck dissections and the inherent morbidity associated with it. The early validation trials of this technique have been promising,[98,99] with more recent reports of the rate of neck recurrence following SLNB of <5% with no decrease in survival, and prevented as many as 70% of patients from undergoing unnecessary elective neck dissection.[100–103] The completion of additional multicentered prospective trials will determine the ultimate utility of this technique.

POSTTREATMENT SURVEILLANCE

After successful treatment of cancer in the oral cavity, appropriate posttreatment surveillance is critical to identify recurrence of cancer and second primary lesions in patients with the risk profile for oral cavity malignancy. Clinical examination at 3-month intervals is generally recommended for the first 2 years following treatment. The interval may be increased in subsequent years (4 to 6 months) for a total of 5 years.[104] Patients at high risk and with current environmental risk factors such as tobacco and alcohol use may require lifelong surveillance. In addition to basic laboratory tests, imaging studies such as a CT, PET-CT, or MRI are also critical for surveillance. The interval of imaging studies and the type of study varies depending on the initial primary site, disease factors, and the length of time elapsed since the initial therapy.[105] In general, PET-CT offers a combination of functional and anatomical imaging, which is excellent for oral cavity cancers; however, contrast CT scan may also be used. PET-CT offers excellent negative predictive value for tumor surveillance but does have issues with specificity; however, PET-CT has been shown to provide valuable data, which may alter the management of patients in this population.[106,107] MRI is helpful for patients with significant dental or hardware artifact and offers superior soft tissue resolution. The role of PET-MRI is currently under investigation.[108]

Perhaps the most important factor in the posttreatment surveillance of patients treated for malignancy of the oral cavity is the onset of new symptoms. Pain, numbness, bleeding, motor nerve deficits, infections and fistula without obvious sources, and new-onset dysphasia or dyspnea should

prompt the clinician to entertain the possibility of recurrent disease and perform the necessary workup.

CONCLUSION

Oral cavity cancer continues to challenge physicians worldwide. Locoregional control continues to be a difficult task, and improvements on disease-free survival over the last 50 years have been minimal. Patients continue to suffer from the effects of these malignancies and the therapy currently used to treat them. Future investigations should yield strategies that provide improved cure rates, with improved quality of life, for this challenging patient population.

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14 Cancer of the Oropharynx

David M. Neskey Katherine A. Hutcheson Michael E. Kupferman

Nearly 10,000 cases of cancer of the oropharynx are diagnosed each year in the United States.[1] Previously, these cancers had a strong association with chronic alcohol and tobacco use, but over the past decade, the increasing incidence of the human papillomavirus (HPV) has been identified as a major etiologic agent of the oropharynx cancer.[1,2] HPV-associated squamous cell carcinoma (SCC) is now the predominant histologic type found in the oropharynx although non–HPV-associated SCC subtypes and minor salivary gland cancers are seen but less frequently.

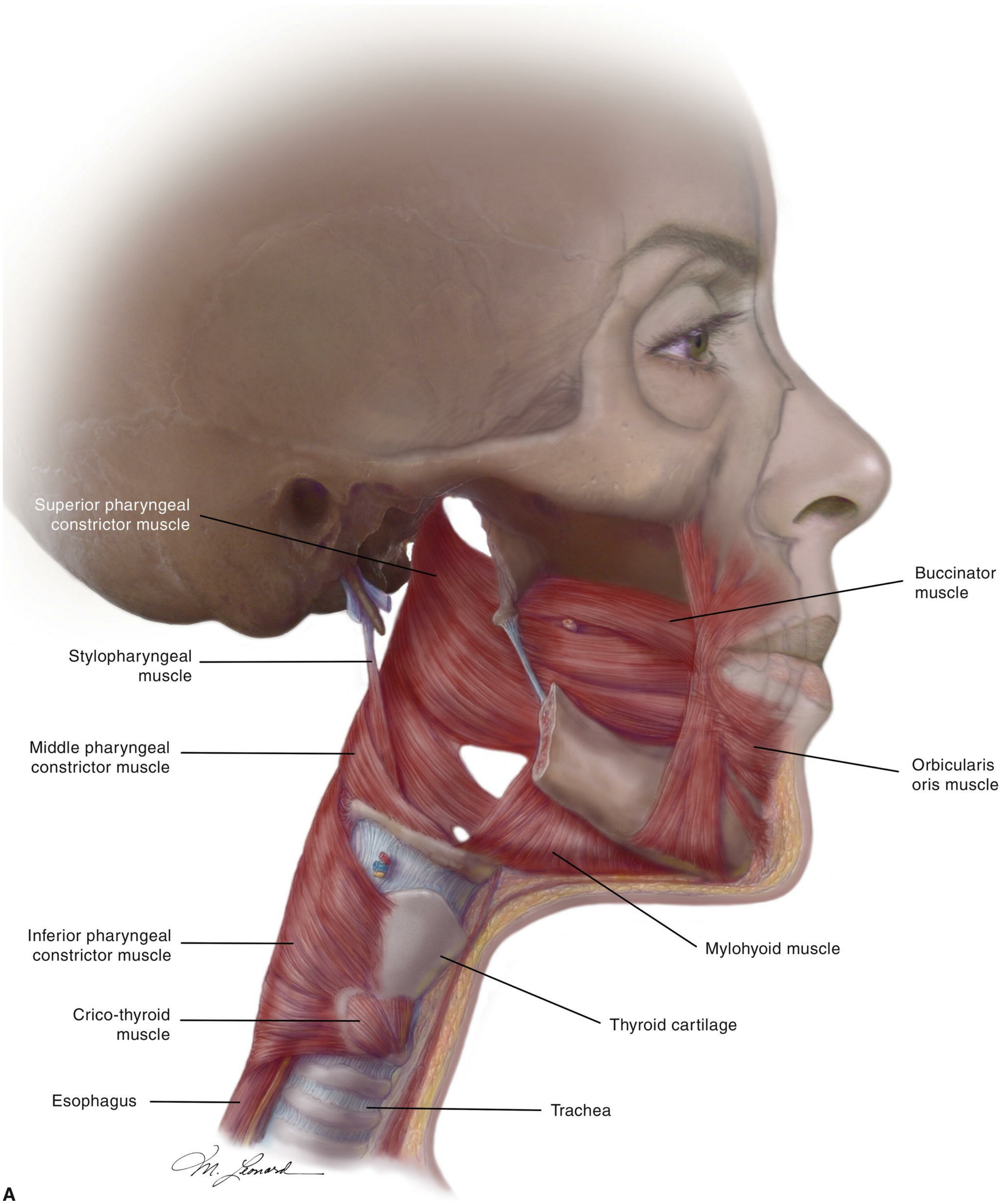
Cancer of the oropharynx represents a diagnostic and therapeutic challenge because of the key role that the anatomic region plays in the normal function of speech, swallowing, and breathing, which requires an individualized, multidisciplinary approach for management. Head and neck surgeons, radiation and medical oncologists, speech pathologists, and dental oncologists must work in concert toward the goals of eradicating the disease, preserving function, and, when needed, functionally rehabilitating these patients after treatment. Because these cancers are frequently deeply invasive and/or present with extensive regional lymph node metastases, local–regional control is the primary therapeutic goal. Patients with HPV-associated SCC have improved survival rates compared to their non–HPV-associated counterparts, for whom overall survival rates have not improved dramatically over the past 30 years.[3,4] Advances in both radiation therapy (RT) with the advent of intensity-modulated RT and surgical approaches with laser microsurgery and robotic surgery will hopefully continue to improve survival rates while decreasing the short- and long-term morbidity. Finally, as prognostic and predictive biomarkers become validated in clinical practice, the management of oropharyngeal cancers will hopefully become more individualized.

ANATOMY

Boundaries

The oropharynx is a three-dimensional structure bounded anteriorly by the anterior tonsillar pillars (the palatoglossus muscle), the circumvallate papillae (sulcus terminales), and the junction of the hard and soft palate. Posterior and lateral boundaries are formed by the muscular pharyngeal wall (superior and middle constrictors). The superior extent is the level of the soft palate (some define this as the level of the hard palate). The inferior extent is to the vallecula at the level of the hyoid. The oropharynx is further subdivided into five areas, which include the lateral pharyngeal walls, tonsillar regions, posterior wall, base of the tongue, and soft palate. Additionally, the pharynx consists of six major muscles, the superior pharyngeal constrictor, middle pharyngeal constrictor, inferior pharyngeal constrictor, stylopharyngeus, salpingopharyngeus, and palatopharyngeus.

Cancer arising in the oropharynx can extend laterally or posteriorly to involve the parapharyngeal or retropharyngeal spaces, respectively. Lateral extension through the superior constrictor muscle can involve any of the structures of the poststyloid compartment of the parapharyngeal space including the carotid artery, jugular vein, cranial nerves IX through XII, and the sympathetic chain. The posterior pharyngeal wall begins at the Passavant ridge of the superior constrictor. The layers of the posterior pharyngeal wall are critical to the understanding of the spread of cancer in this area and include mucosa, submucosa, superior constrictor, pharyngobasilar fascia, and prevertebral fascia. The pharyngobasilar fascia is a natural barrier to the spread of cancer and is separated from the prevertebral fascia by areolar tissue. Posterior extension of cancer through the muscles and into the pharyngobasilar fascia, but not the prevertebral fascia, can still allow a complete surgical resection with clear margins. In contrast, once the prevertebral fascia is involved, or is fixed to the vertebral bodies, the cancer is no longer considered to be resectable (**Fig. 14.1A–C**).


Superior pharyngeal constrictor muscle
Buccinator muscle
Stylopharyngeal muscle
Middle pharyngeal constrictor muscle
Orbicularis oris muscle
Inferior pharyngeal constrictor muscle
Mylohyoid muscle
Crico-thyroid muscle
Thyroid cartilage
Esophagus
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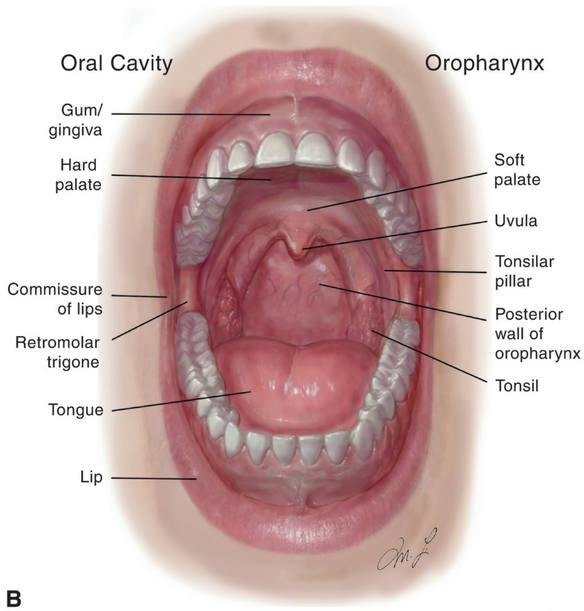

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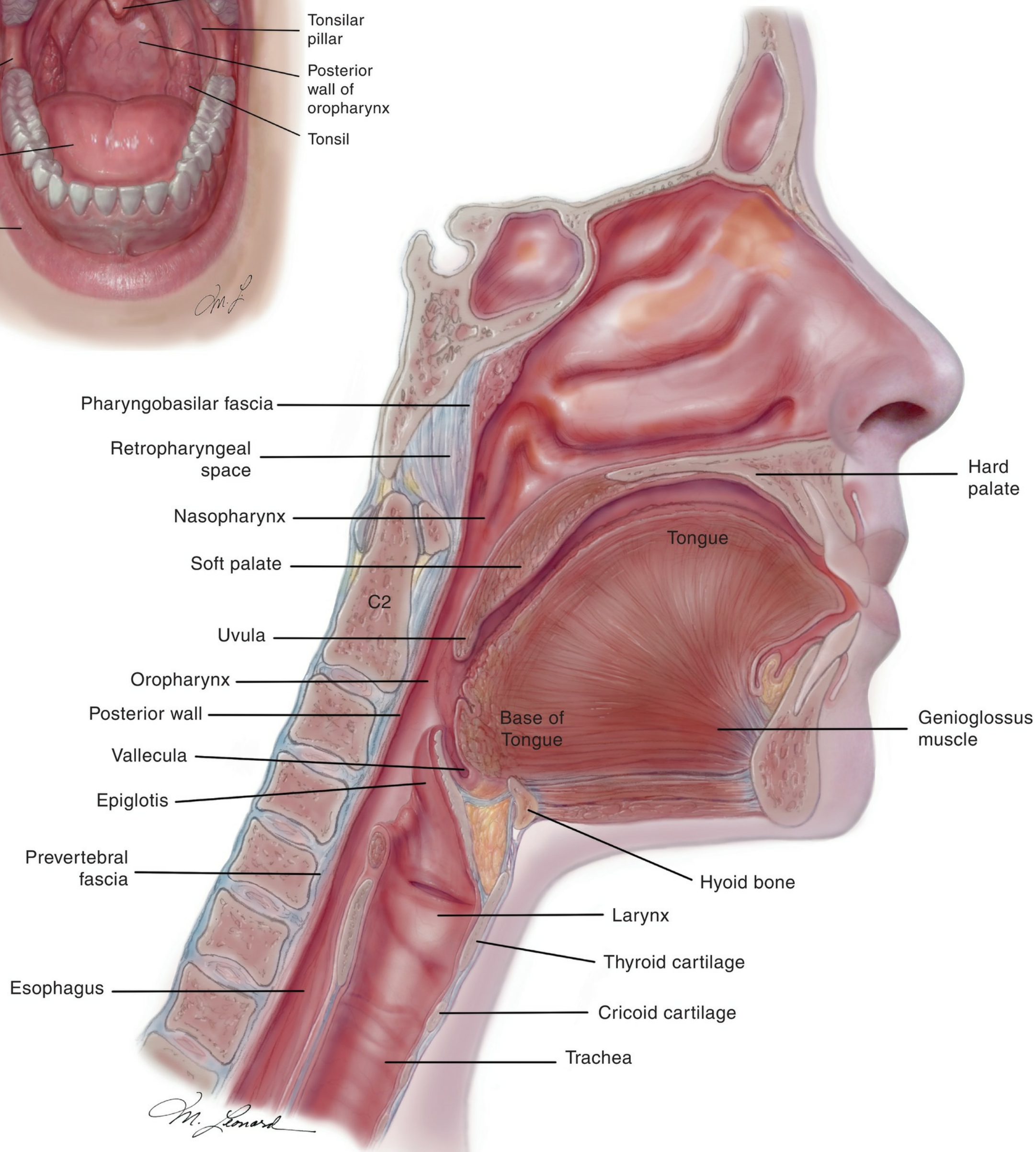


C

Figure 14.1. A–C: Anatomic boundaries of the oropharynx.

The base of the tongue extends from the circumvallate papillae to the vallecula at the base of the epiglottis and encompasses the glossoepiglottic and pharyngoepiglottic folds. Superiorly and laterally, the base of the tongue

extends to the glossopalatine sulcus and the glossopharyngeal folds inferiorly and laterally.

Innervation

Most of the sensory innervation of the pharynx is derived from the glossopharyngeal nerve (cranial nerve IX), specifically through its pharyngeal and tonsillar branches. The pharyngeal branch arises prior to the glossopharyngeal nerve traveling intimately with the stylopharyngeus muscle. The pharyngeal branch then merges with the pharyngeal branch of the vagus nerve (cranial nerve X), which then proceeds to the pharyngeal plexus located within the external fascia of the pharynx. Although the pharyngeal branch provides most of the sensory innervation, the tonsillar branch of the glossopharyngeal nerve directly supplies the oropharyngeal isthmus as it communicates with the lesser palatine nerve (from cranial nerve V2). The soft palate receives its innervation from the lesser palatine branch of the maxillary nerve. The six major muscles of the pharynx all derive motor input from pharyngeal and superior laryngeal branches of the vagus nerve (cranial nerve X) through the pharyngeal plexus, except the stylopharyngeus. Instead, the stylopharyngeus muscle derives motor innervation from the glossopharyngeal nerve (cranial nerve IX) from fibers of the nucleus ambiguus (**Fig. 14.2**).

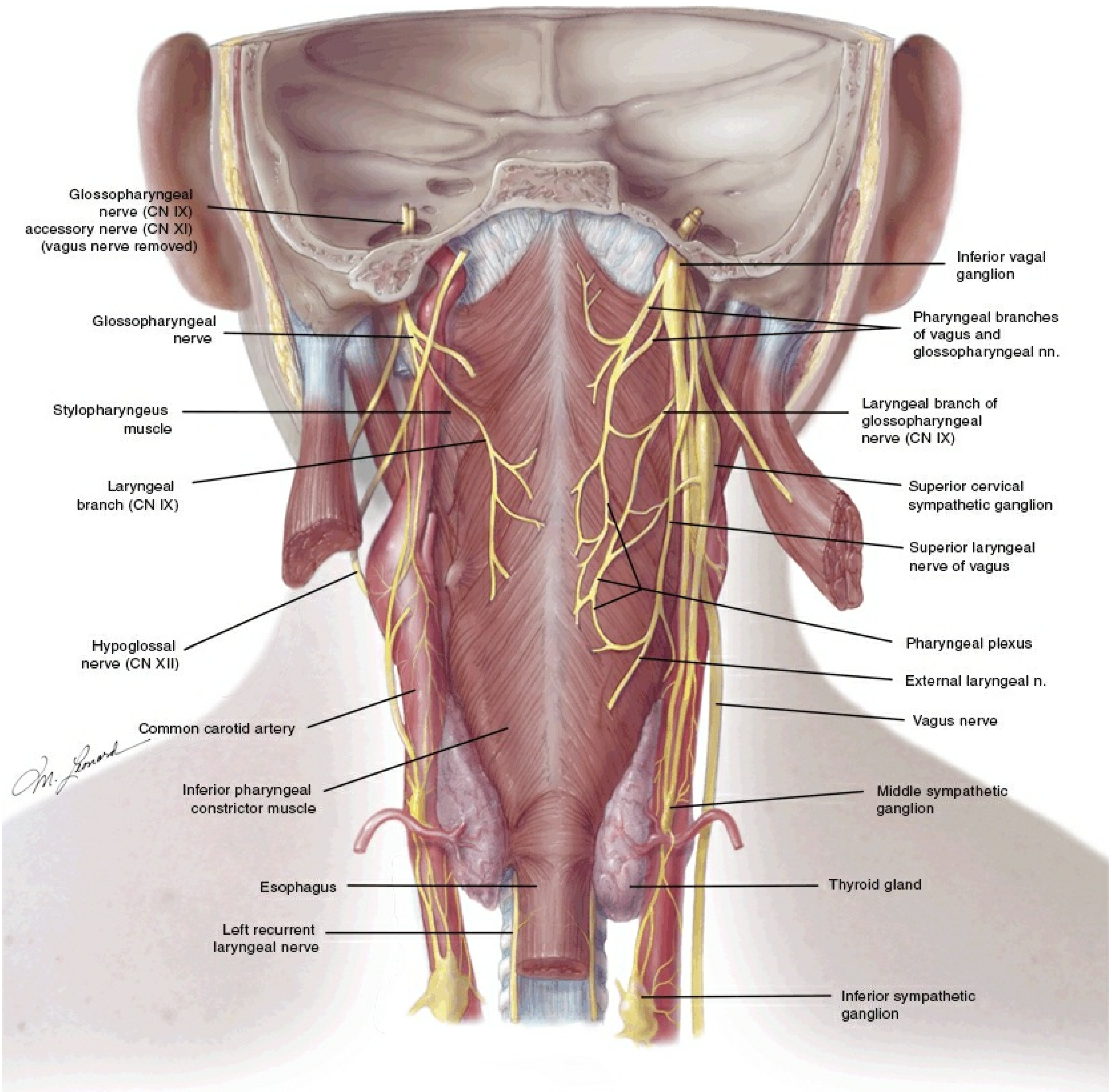


Figure 14.2. Innervation of the oropharynx.

Vasculature

The pharynx receives its blood supply from several sources. The superior aspect of the pharynx receives blood from the pharyngeal branch of the ascending pharyngeal artery and descending branches of the lesser palatine arteries. The inferior aspect of the pharynx receives blood supply from the inferior thyroid artery and superior thyroid artery. The rest of the pharynx receives blood from the ascending palatine and tonsillar branches of the facial

artery as well as from the maxillary artery. The internal carotid artery, which is an essential surgical landmark, lies deep to the superior constrictor muscles and medial to the medial pterygoid muscle. It is generally covered in adipose tissue within the prevertebral fascia[5] (**Fig. 14.3**).

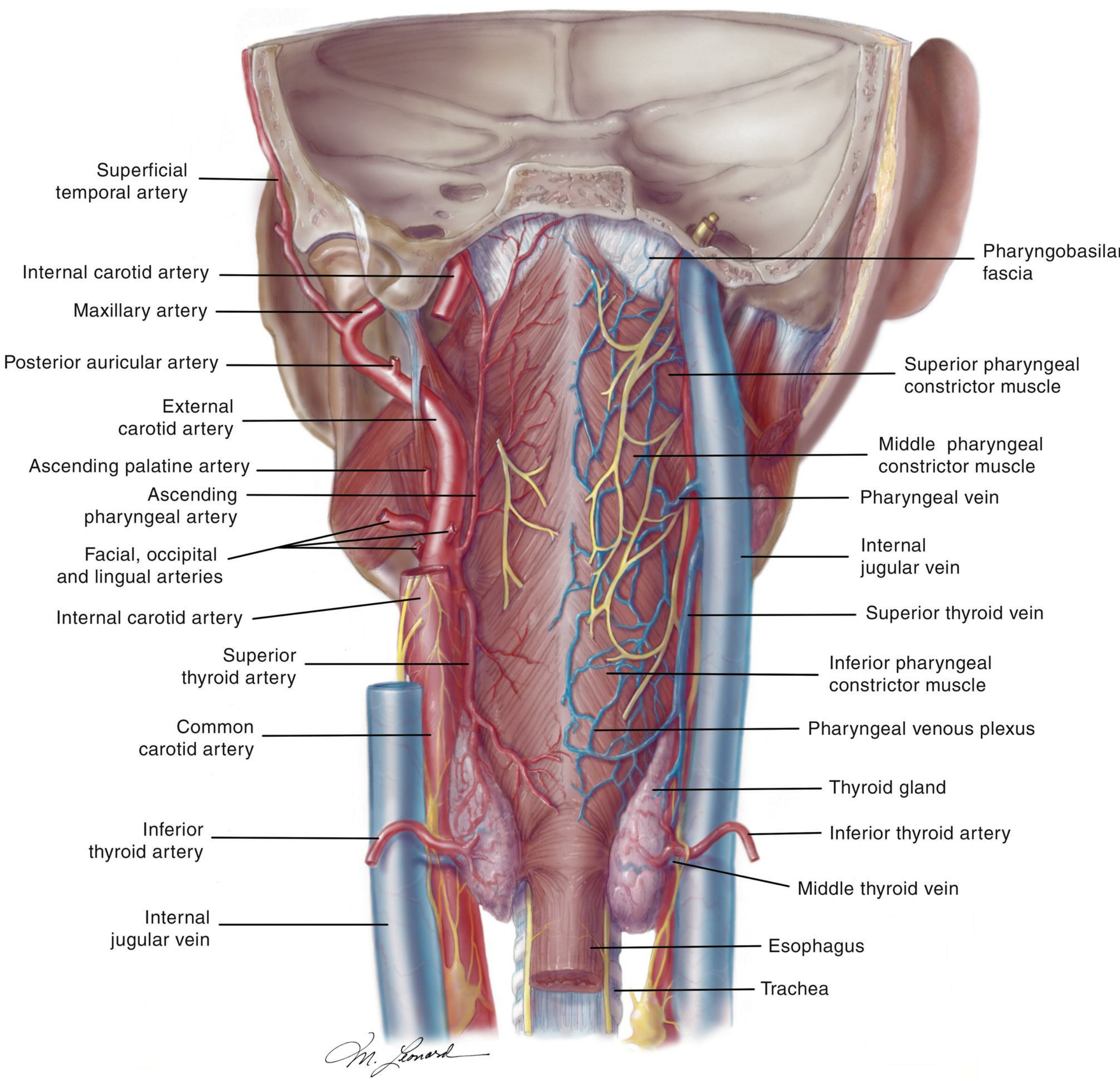


Figure 14.3. Vascular supply of the oropharynx.

Lymphatics

The lymphatic drainage of the oropharynx varies greatly across the different subsites, but the two lymph node basins most frequently involved are the

internal jugular nodes and the retropharyngeal nodes. The base of the tongue has both superficial and deep lymphatic networks that are bilateral in up to 30% of patients. The primary lymph nodes involved in primary cancer of the base of the tongue are levels II–IV. The tonsil drains to the lateral retropharyngeal lymph nodes and ipsilateral level II–III nodes. The soft palate has three distinct drainage systems, anterior, middle, and posterior. The anterior system drains primarily the hard palate and the anterior aspect of soft palate and involves the level I lymph nodes. The middle system can drain bilaterally, most commonly to level II at the posterior belly of the digastric. The posterior system can also drain bilaterally to the retropharyngeal nodes via penetration of the lymphatics through the superior constrictor muscles.[6]

EPIDEMIOLOGY, RISK FACTORS, AND PREVENTION

SCC of the oropharynx, like tumors from other head and neck subsites, has been traditionally associated with tobacco and alcohol consumption. In contrast to nonoropharyngeal cancers, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) has increased in recent decades, specifically among younger age groups.[7–11] This decline in incidence of nonoropharyngeal cancers may be attributed to reductions in tobacco use in the United States, whereas the rising incidence of oropharyngeal cancers is due to a higher incidence of infection with HPV.[1,12]

The prevalence of HPV in OPSCC in the United States has steadily increased from <20% in the 1980s to over 70% in 2004, with palatine and lingual tonsils most frequently involved.[1,3] With a conservative estimate that 70% of OPSCC are HPV positive, it is projected that over 11,300 new cases will be diagnosed in the United States in 2020, and by 2030, 47% of all HNSCC will originate from the oropharynx[1] (**Fig. 14.4**). This increase in OPSCC has also been observed in other countries, specifically Canada, Slovakia, the Scandinavian countries, and Greece.[13–17] The risk factors associated with HPV-associated OPSCC are distinct from HPV-negative tumors and include oral sexual behaviors and marijuana use, whereas HPV-negative tumors are associated with poor dental hygiene and tobacco and alcohol use.[18] Furthermore, a dose–response relationship has been identified

between the risk of developing HPV-positive OPSCC with number of oral sex partners and joint years of marijuana use.[18]

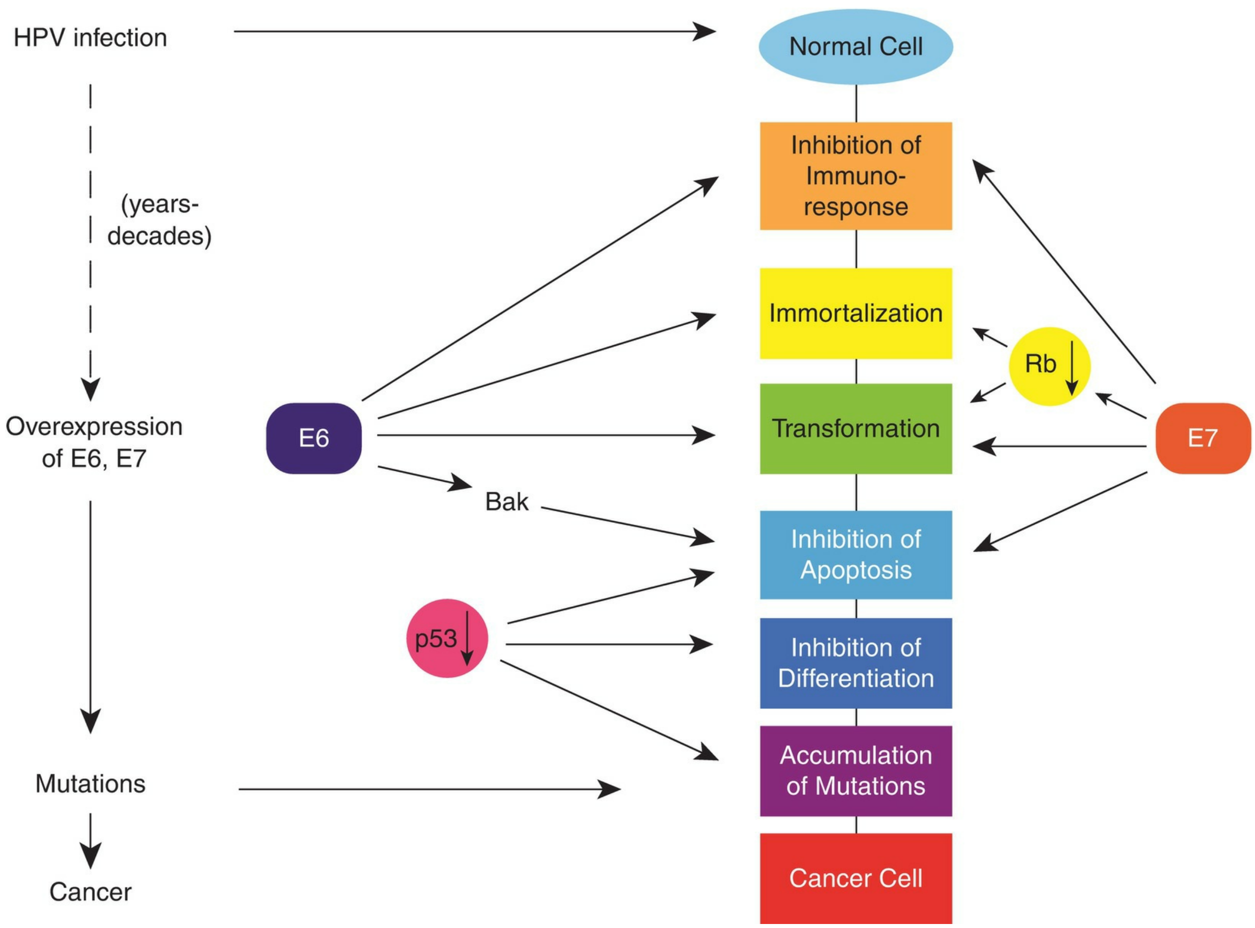


Figure 14.5. The mechanisms of HPV oncogenes E6 and E7 in cancer development.

HPVs are DNA viruses with a unique affinity for human epithelia, and HPV-associated cancers typically arise from the palatine or lingual tonsillar crypts de novo without clear evidence of epithelial dysplasia. Over 120 different HPV types have been isolated, with low-risk types (e.g., HPV 6, 11) inducing benign hyperproliferation of the epithelium, leading to lesions such as papillomas and warts. High-risk types (e.g., HPV 16, 18, 31, 33, 35) are defined by epidemiologic associations with cervical cancer.[19] The prototypical oncogenic types 16 and 18 account for over 90% of HPV-related OPSCC and are capable of malignant transformation of primary human keratinocytes from either genital or upper respiratory tract epithelia.[20] This transforming potential is attributed to two HPV oncoproteins, E6 and E7, that

inactivate two human tumor-suppressor proteins, p53 and pRb, respectively. These viral oncoproteins lead to transformation through the stimulation of cellular proliferation, delay of cellular differentiation, increase in the frequency of spontaneous and mutagen-induced mutations, and promotion of focal and broad chromosomal instability in transfected cell lines[21] (**Fig. 14.5**). Furthermore, in order to maintain a malignant phenotype, a transcriptionally active viral genome appears to be necessary.[22]–[25]

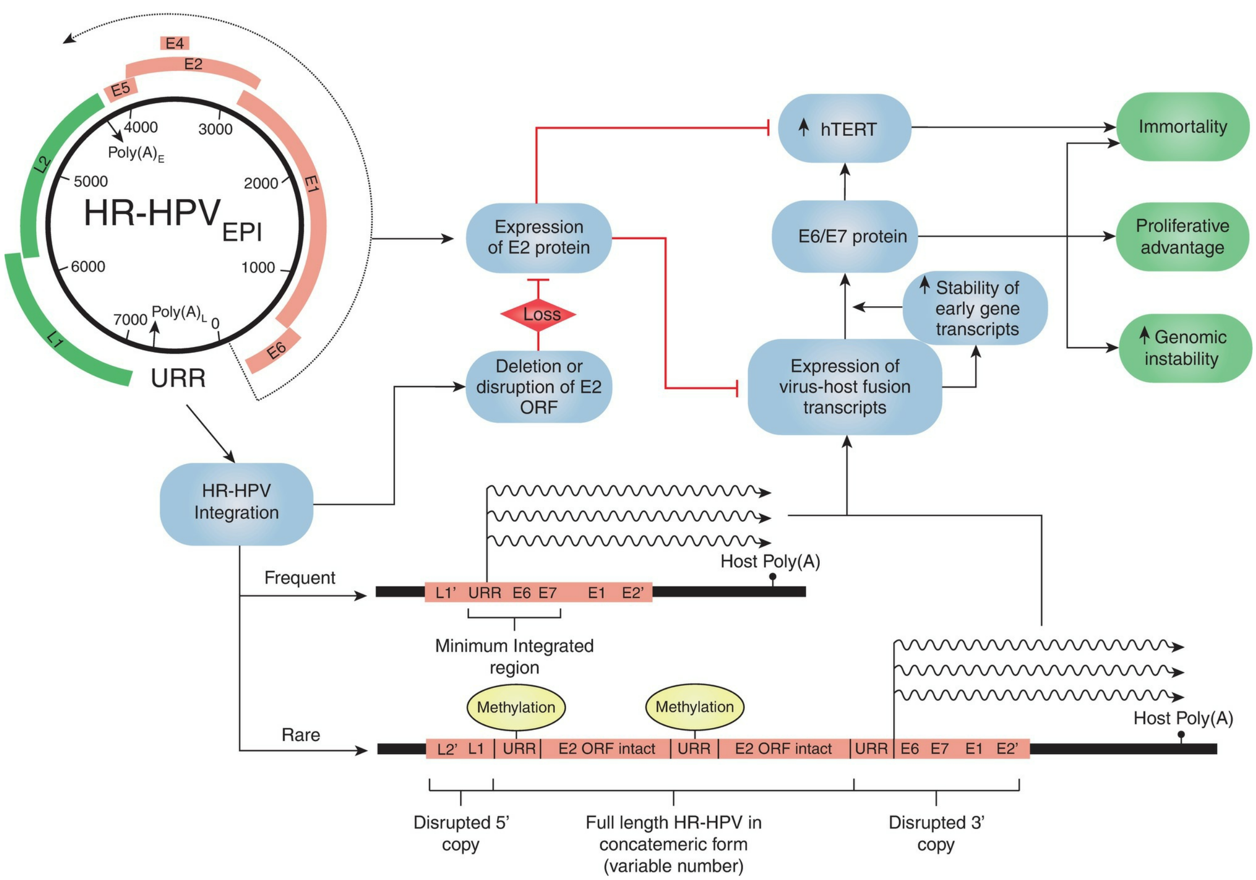


Figure 14.6. Significance of HR-HPV integration events detected in cervical carcinomas. The majority of integrants that derive from insertion of HR-HPV episomes ($\text{HR-HPV}_{\text{EPI}}$) into the host genome are detected at low copy number and retain at least the E6 and E7 oncogenes together with the viral upstream regulatory region (URR). Integrant copy number is often increased through amplification of viral and flanking host DNA. Typical integrants also have complete or partial disruption of the ORF for E2, the viral gene that regulates viral replication and which, by binding sites in the URR, can inhibit expression from integrated virus. Disruption of the viral genome also dissociates viral early (E) gene transcription from the viral early

polyadenylation signal, leading to use of host poly(A) signals and transcription of virus–host fusion transcripts with a longer half-life. These events lead to increased levels of E6 and E7 proteins, which, together with loss of additional inhibitory effects of E2, result in cellular immortalization, deregulated proliferation, and increased genomic instability. More rarely, concatemeric integrants are observed, where viral copies (including intact E2) are arranged in a head-to-tail fashion with partially deleted copies at the 5 and 3 ends. Note that the dashed line in the figure represents transcription from the early promoter of HR-HPVEPI (P97 in HPV16). (Adapted from Pett M, Coleman N. Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? *J Pathol.* 2007;212(4):356–367, with permission.)

In the normal viral life cycle, the genome replicates as episomally.[26] In cervical lesions, the HPV genome is consistently retained in the episomal state in early dysplasia and low-grade lesions, but integration of the viral genome into the host chromosome is associated with high-grade lesions and the majority of HPV-associated cervical carcinomas.[27–29] This integration appears to be a direct consequence of host chromosomal instability and is an important molecular event in the progression from high-grade lesions to invasive carcinoma.[30] A possible explanation for this disease progression is the dysregulation of the viral oncogenes following integration due to complete or partial loss of E2 open reading frame (ORF).[30] This hypothesis is supported by the finding that E6 and E7 confer a much stronger transforming capacity in primary cells following integration compared to episomal transcripts.[31] The HPV integration sites are randomly distributed throughout the host genome with a clear preference for genomic fragile sites. Viral integration is a consequence of an overall destabilization process of the chromosomal integrity in replicating epithelial cells that express the viral E6 and E7 genes. Therefore, alterations in the viral genome secondary to integration and the impact of the host cellular sequences on transcriptional regulation of the viral genes appear to be more important than cellular alterations due to the HPV integration[26,30] (**Fig. 14.6**).

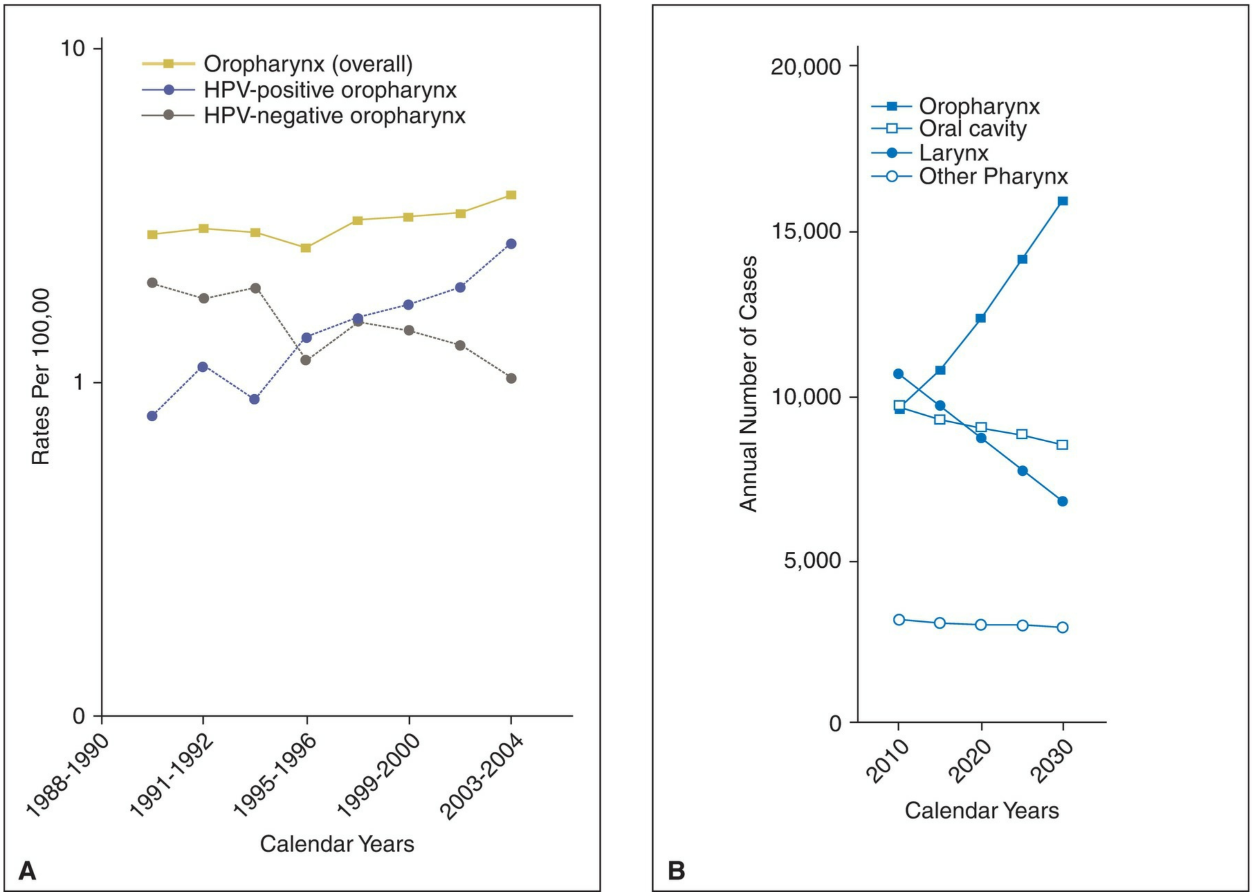


Figure 14.6. A: Incidence rates for oropharyngeal cancer (overall), HPV-positive oropharyngeal cancer, and HPV-negative oropharyngeal cancer. **B:** Projected annual number of patients with oropharyngeal, oral cavity, laryngeal, and other pharynx cancers through the year 2030. Observed incidence rates during 1973 to 2007 from nine registries within the Surveillance, Epidemiology, and End Results (SEER) program were used in age-period-cohort models to project expected incidence through the year 2030. (Adapted from Mehanna H, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer-systematic review and meta-analysis of trends by time and region. *Head Neck.* 2013;35(5):747–755. http://dx.doi.org/10.1002/hed.22015. PubMed PMID: 22267298, with permission; and data from Chaturvedi, AK, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29(32):4294–4301.)

The increasing incidence of HPV-positive OPSCC raises important public health considerations, which utilizes health promotion and primary prevention strategies aimed to decrease the incidence of this disease. The

prevalence of oral HPV-16 infection is 1% in the United States and has been associated with a 50-fold increased risk for HPV-positive OPSCC.[18,32] In the primary care setting, risk factor modification including reduction in high-risk sexual behavior, decreased oral HPV infection, and smoking cessation should be discussed with patients.

Because HPV-positive OPSCC is related to only a few high-risk HPV subtypes, the potential exists for prevention of this disease through vaccination targeting those subtypes.[32,33] Unfortunately, vaccination is effective only prior to infection, because it induces neutralizing antibodies that prevent virion entry but does not halt the progression of existing lesions; therefore, vaccination must occur at a young age.[34,35] The two vaccines (HPV bivalent29 and quadrivalent30 vaccines) approved by the U.S. Food and Drug Administration (FDA) prevent persistent cervical HPV-16 infection.[35] The bivalent vaccine is indicated for the prevention of cervical cancer in women, whereas the quadrivalent vaccine has an additional approval for the prevention of genital warts and genital cancers in both genders up to 26 years of age. The Advisory Committee on Immunization Practices first recommended in 2007 that girls 11 to 12 years of age be vaccinated with the quadrivalent HPV vaccine. The recommendation was updated in 2011 that boys aged 11 or 12 years should also be vaccinated with three shots.[36] Females 13 to 26 years of age and males 13 to 21 years of age who were not previously vaccinated are recommended to be vaccinated. Because there is no screening strategy for OPSCC, vaccination may have higher impact in OPSCC than in cervical cancer, given that the incidence is estimated to surpass that of cervical cancer by 2020.[1] Parents of children of both sexes should be informed that vaccination is available, and, although not approved for this indication, it may reduce the risk of other HPV-related cancers, including OPSCC.

PATHOLOGY

As mentioned previously, the oropharynx is divided into subsites that are lined with distinct epithelial types. The posterior pharyngeal wall, which begins at Passavant ridge, transitions from ciliated respiratory epithelium of the nasopharynx to nonkeratinizing stratified squamous epithelium of the oropharynx. The lymphoepithelium of Waldeyer ring is formed by the fusion

of the overlying stratified squamous epithelium that extends into the deep tonsillar crypts within the underlying lymphoid tissue.[37] Minor salivary glands are located throughout the submucosa of the oropharynx.

SCC accounts for over 90% of the malignant neoplasms in the head and neck. Although SCC of the head and neck has classically been considered a homogeneous disease, recent epidemiologic trends and molecular profiling have identified distinct subtypes.[18,38] With the emergence of HPV-associated OPSCC, the typical differentiated keratinizing and nonkeratinizing SCC of the head and neck represents an increasingly smaller proportion of neoplasms in the oropharynx. Tumors of this histology tend to arise in older patients with a history of tobacco and alcohol abuse.[4]

Non–HPV-Related Squamous Cell Carcinoma

Keratinizing SCC tends to be fungating and ulcerative with limited submucosal spread but infiltrating margins. The presence of intracellular and extracellular keratin is common, and the cells are large and have the characteristic intracellular bridges.[36] Nonkeratinizing SCCs occur less frequently than do their keratinizing counterparts and grow in broad connecting bands resembling a plexus with cells that contain prominent nucleoli.[36]

Basaloid SCC is a rare but aggressive subtype of SCC that primarily arises in the base of the tongue. This cancer has a propensity for submucosal spread with central ulceration and is composed of tightly packed moderately pleomorphic cells that form cords and nests. Patients typically present with late-stage disease including regional and distant metastases.[36]

Spindle cell carcinoma is a fusion between classic SCC with spindle cells and can be referred to as sarcomatoid carcinoma. The spindle cell component tends to form the bulk of the tumor with the SCC being restricted to the stalk or base. These cancers will stain for both epithelial markers including keratin and mesenchymal markers including vimentin.[39]

Lymphoepithelial carcinoma is histologically identical to undifferentiated nasopharyngeal carcinoma (WHO III). Cancer cells are typically surrounded by lymphocytes and have large vesicled nuclei that are positive for cytokeratin. Like NPC, these cancers tend to arise in younger patients, are not

associated with alcohol or tobacco, and are radiosensitive.[40]

HPV-Related OPSCC

The pathologic features of HPV-related SCC of the oropharynx are distinct from those of the keratinizing differentiated SCC that arises from the other head and neck sites. The unique histologic features include lesions that arise from the tonsillar crypts without associated dysplasia of the epithelial surface. Additionally, these cancers exhibit lobular growth and are infiltrated with lymphocytes. Finally, the cells lack significant keratinization and demonstrate a prominent “basaloid” morphology.[41] There are two microscopic features of HPV-related oropharyngeal cancers that are frequently misunderstood. First, these cancers are frequently described as poorly differentiated based on immature appearance of the cells, when in fact these cells closely resemble the reticulated epithelium of the tonsillar crypts and are actually highly differentiated.[42] Second, the “basaloid” descriptor can be misleading and associate these cancers with aggressive basaloid SCC subtype. Although these two SCCs look similar morphologically, the detection of HPV results in significantly improved survival outcomes relative to the HPV-negative basaloid SCC.[43]

Minor Salivary Gland

Tumors of the minor salivary glands represent fewer than 10% of neoplasms in the oropharynx, but unlike tumors of the major salivary glands, the majority of tumors are malignant.[44,45] The majority of minor salivary gland tumors arise in the base of the tongue, followed by the soft palate and palatine tonsil.[46] The histologic heterogeneity in the minor salivary glands mirrors that of the major salivary glands, with adenoid cystic and mucoepidermoid carcinomas being the most frequent. There are conflicting data as to which neoplasm is actually the most frequent, but a recent series that focused on minor salivary gland malignancies of the oropharynx identified mucoepidermoid carcinomas as the most frequent, followed by adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and carcinoma ex-pleomorphic adenoma.[46]

DIAGNOSIS

History

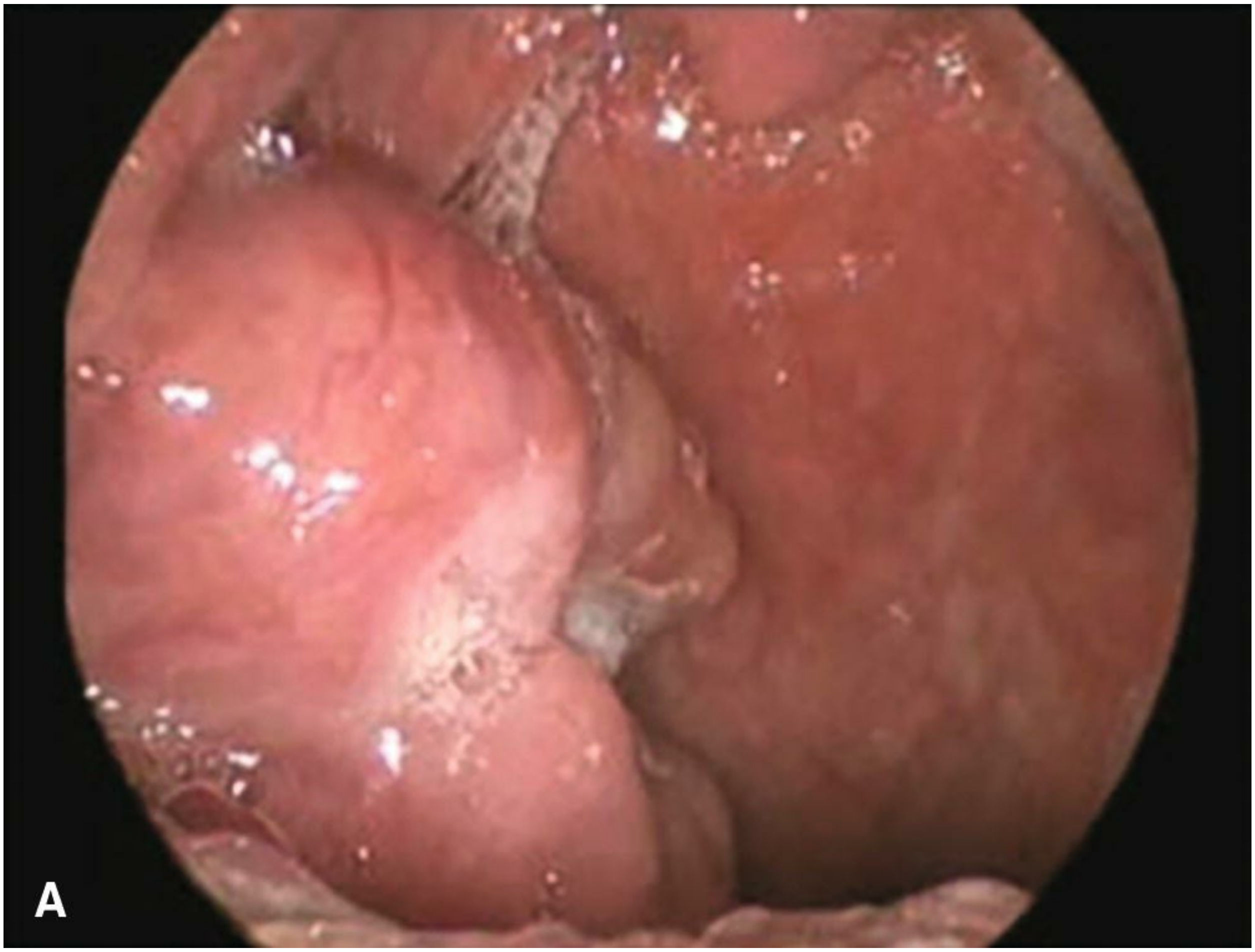
A complete history including review of systems, personal and family history of cancer, social history, and sexual history needs to be documented. As mentioned previously, the risk factors associated with HPV-positive tumors are distinct from HPV-negative tumors. Marijuana use of >1 cigarette per day for at least 5 years and >11 vaginal sex partners or 6 oral sex partners are most closely associated with HPV-positive OPSCC.[18] In contrast, the risk of developing HPV-negative OPSCC is associated with being a current smoker, a >20 pack-year history of tobacco smoking, and >14 drinks per week for 50 years.[18] Because of these differences in risk factor profiles, a thorough history needs to be gathered because of the HPV status of the cancer at presentation.

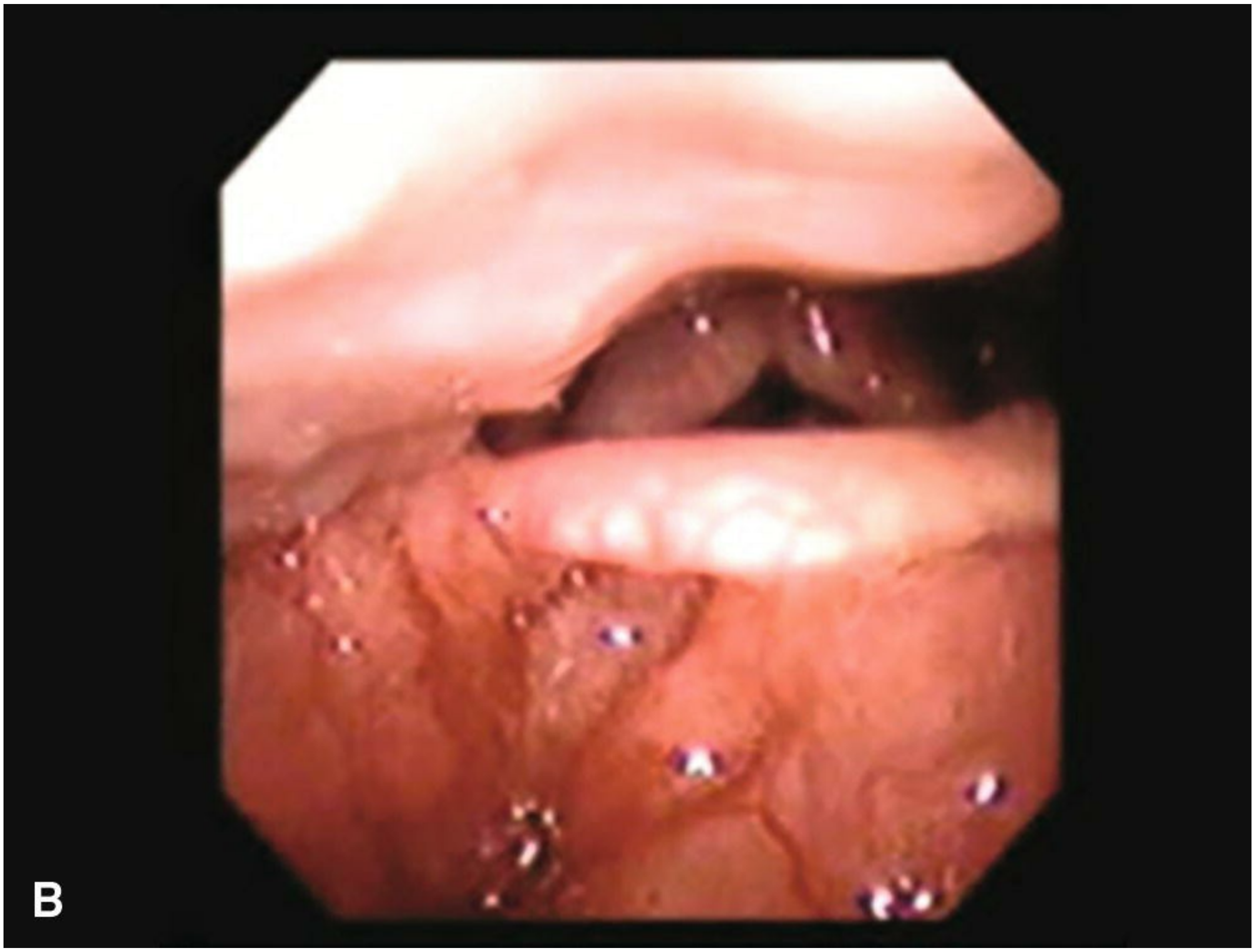
The presenting symptoms also differ between HPV-positive and HPV-negative tumors. Patients with HPV-positive tumors typically have smaller primary cancers and therefore rarely have local symptoms at presentation but will often have a painless mass in the neck secondary to regional metastases.[47] In contrast, patients with HPV-negative cancers tend to have a greater disease burden at the primary site, which results in more local symptoms of pain, otalgia, and dysphagia.

Physical Examination

A complete examination of the head and neck should be performed on all patients. Systematic inspection of all the mucosal surfaces of the upper aerodigestive tract is necessary because of the field cancerization phenomenon that can lead to synchronous primaries, particularly in the patient with non-HPV–associated cancer.[48] Visual inspection of the base of the tongue and larynx is greatly facilitated with a fiberoptic nasopharyngoscope (**Fig. 14.7A–D**). In addition to inspection of the mucosal surfaces, the tonsils and base of the tongue must be palpated to assess the extent of the tumor and for any submucosal spread. Moreover, the extent of the lesion into the deep tissues of the base of the tongue, vallecula, and glossopharyngeal sulcus is often only evident upon palpation. Assessment of the mandible range of motion and a thorough examination of the cranial nerves also must be performed, with an emphasis on sensation of the lower face and tongue, along with mobility of the tongue and palate. Cranial nerve

deficits or the presence of trismus implies local invasion into the mandible or masticator spaces. All levels of the neck must be evaluated bilaterally, given the rich lymphatic network that drains the oropharynx and the high incidence of metastasis to the cervical lymph nodes.

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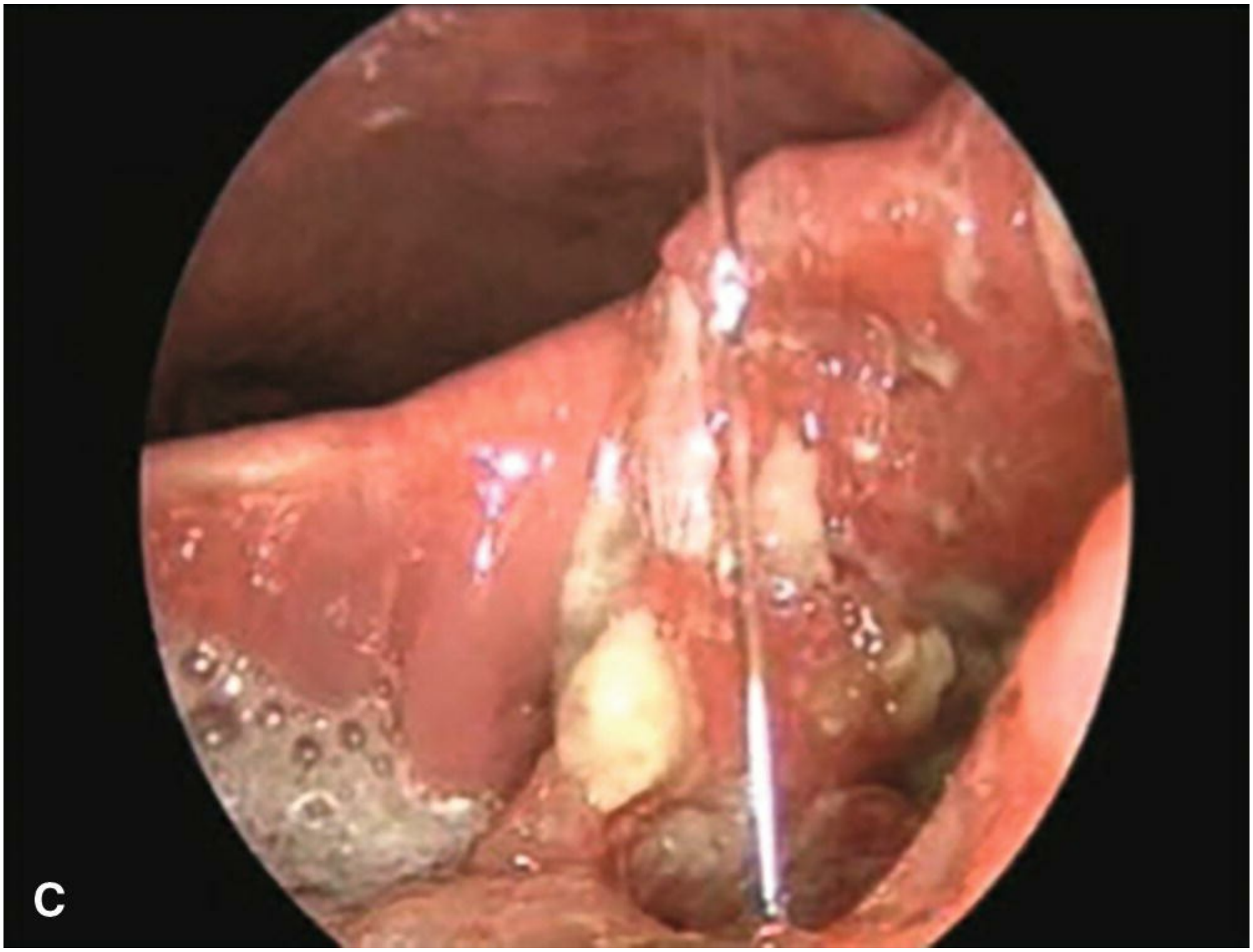
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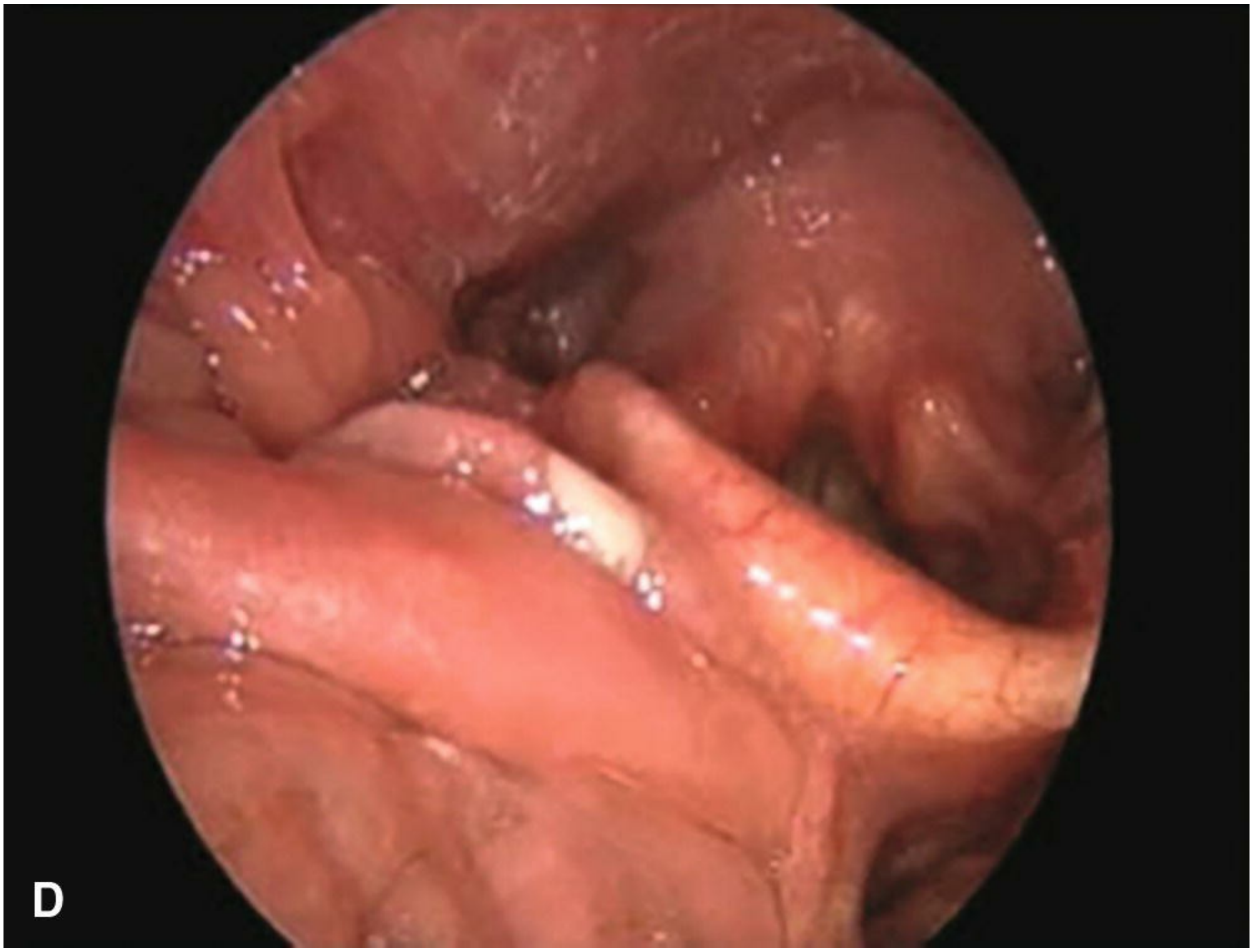

Figure 14.7. Examination of the oropharynx through direct transoral visualization (**A**) or flexible nasopharyngoscopy (**B–D**). Normal appearance of the base of the tongue and vallecula (**B**). Exophytic neoplasm along the glossopharyngeal sulcus (**C**). Small exophytic lesion of the vallecula (**D**).

Diagnostic Imaging

1. Computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in determining the extent of disease at the primary site or regionally. They are primarily indicated in the assessment of advanced-stage cancers where there is concern for involvement of the mandible, parapharyngeal space, prevertebral fascia, cervical nodes, or retropharyngeal nodes. CT scans are better able to evaluate bony structures and cervical lymphadenopathy, whereas MRI is better at evaluating soft tissue, such as the base of the tongue, parapharyngeal space, or prevertebral fascia.
2. Chest radiograph is useful as a screening for metastasis to the lungs,

second primary cancers, and chronic changes associated with the use of tobacco. If a patient presents with significant lymphadenopathy that is in the inferior aspect of the neck (levels IV or VB) or bilateral in nature, a CT of the chest to detect lung metastases should be considered.

3. A panorex is a study complementary to the CT scan for the detection of mandibular involvement, and it is also critical in the assessment of the dentition prior to radiation therapy.
4. Positron emission tomography (PET) in conjunction with a contrast-enhanced CT of the neck can provide accurate anatomic details along with the biologic function about the primary tumor and regional disease. Because HPV-associated SCC frequently presents with smaller primary cancers and the nodal metastases are commonly cystic in nature, the additional functional characteristics provided by the 18F-FDG PET can improve the initial staging of these patients.[3,49,50] Furthermore, although an increased frequency of distant metastases is not related to HPV status, HPV-associated OPSCC tends to disseminate to multiple organs that are not typically involved in non–HPV-associated metastatic HNSCC.[51] These metastases also can manifest later in the course of the disease between 3 and 5 years after completion of treatment.[51] Due to this atypical pattern of disease spread, initial and surveillance imaging needs to assess distant sites of disease. The benefit of PET/CT relative to a contrast-enhanced CT in the assessment of treatment response is still not clear. One of the challenges is the timing of the posttherapy PET/CT. The optimum timing after chemotherapy and radiation therapy is not known, but an interval of 12 weeks has generally been recommended to allow for a reduction in the radiation-induced inflammation and therefore improve the accuracy of the test.[52]

Laboratory evaluation of patients with cancer of the oropharynx includes a complete blood count, electrolytes, creatinine, BUN, and liver function tests.

Staging Endoscopy and Biopsy

Patients with primary epithelial cancers of the upper aerodigestive tract should undergo examination under anesthesia independent of the presenting T stage. Direct visualization and palpation of the tumor improve the assessment of submucosal spread and invasion of surrounding structures,

especially in patients presenting with trismus. A thorough examination using direct laryngoscopy for a synchronous second primary cancer is essential, as these lesions can occur in 8% to 12% of patients with history of tobacco use.[48,53] Bronchoscopy can also be performed to evaluate for small distant metastases or second primary cancers of the lung, which have been reported to occur in 2% HNSCC patients independent of stage.[54] The findings from the examination under anesthesia and endoscopy are then used to calculate clinical staging of the primary site.

Approximately 2% to 9% of patients who have cancer of the oropharynx will initially present with cervical lymphadenopathy with an unknown primary.[55] The most common sites of primary lesions are the tonsillar fossa and base of tongue, which account for 82% of cases.[56] Panendoscopy is crucial for these patients and tonsillectomy is recommended if the primary cancer is not identified as up to 25% of unknown primaries are located in this site. Bilateral tonsillectomy is merited in these cases because of a 10% rate of contralateral spread from occult tonsil lesions.[57,58] More recently, transoral robotic surgery (TORS) has been used to identify the unknown primary site in the tongue base in patients who have undergone a panendoscopy and tonsillectomy.[59] The most recent AJCC staging guidelines for SCC of the oropharynx use only tumor size, lymph node involvement, and the presence of distant metastases as predictors of overall survival (**Table 14.1**). Future alterations to the AJCC system will likely include HPV status as a major component of patient staging.

Table 14.1 AJCC Staging for Squamous Cell Carcinoma of the Oropharynx

Tumor (T) Stage			
T1	≤2 cm		
T2	2–4 cm		
T3	>4 cm or extension to lingual surface of epiglottis		
T4a	Invades larynx, extrinsic muscles of tongue, medial pterygoid, hard palate, or mandible		
T4b	Invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, or encases carotid		
Lymph Node (N) Stage			
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest diameter		
N2a	Metastasis in a single ipsilateral lymph node, >3 cm in greatest diameter		
N2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest diameter		
N2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest diameter		
N3	Metastasis in a lymph node >6 cm in greatest diameter		
Overall Stage			
Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0-N2	M0
	T1–T3	N2	M0
IVB	T4b	Any N	M0
	AnyT	N3	M0
IVC	AnyT	Any N	M1

From Weinstein GS, et al. Transoral robotic surgery for advanced oropharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg.* 2010;136(11):1079–1085.Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Laboratory Diagnosis of HPV-Related Tumors

Because the HPV has recently emerged as an important etiological factor in the increasing incidence of oropharyngeal cancer, and as a highly relevant biomarker of treatment outcomes for cancer of the oropharynx, a systematic method of detection is essential. The ideal diagnostic detection methods will either localize the genome of high-risk HPV genome to tumor cell nuclei or demonstrate the expression of viral oncogenes, E6 or E7.[60] The most commonly used methods to achieve these aims are p16 immunohistochemistry and in situ hybridization.[61] p16 immunohistochemistry has emerged as a reliable surrogate marker of HPV-

induced neoplasia of oropharynx. In HPV-positive oropharyngeal carcinomas, transcription of the viral oncoprotein E7 is known to functionally inactivate the *retinoblastoma* (*Rb*) gene product. Disruption of this pathway leads to an upregulation of p16 expression that can be detected by immunohistochemistry.[42] In situ hybridization probes are type specific, and therefore multiple probes are necessary to test a complete tumor genotype. Because 90% to 95% of cancers of the head and neck are related to HPV 16 and to a lesser extent HPV 31, 33, 35, the false negative rate of ISH is low.[62] Direct comparison of p16 immunohistochemical staining and HPV-16 ISH for large numbers of HNSCCs reveals a 24% discordance rate. The discrepancies consistently involve cancers that are negative by HPV16 ISH but p16 positive by immunohistochemistry. About 45% of these cases can be attributed to the presence of some other (non-16) HPV type, as confirmed by wide spectrum ISH. The remaining discrepancies are probably due to false-positive staining of p16, which can be seen in basaloid carcinomas that are not related to HPV infection.[62] To optimize HPV detection, a combination of p16 staining with ISH is the most effective. Because the sensitivity of p16 IHC approaches 100%, this is a reasonable first-line test to confidently eliminate those cases that are HPV negative. HPV16 ISH can then be run as a second-line assay for the p16-positive cases, and given a specificity of nearly 100%, the number of false positives from p16 staining alone will be reduced. The combination of these two assays identifies a subset of cancers that require a more rigorous analysis for non-HPV 16 oncogenic types. This third-line assay can either be consensus ISH probe set or PCR for the detection of transcriptionally active virus. This algorithm accurately detects HPV in the majority of cases, and although some tumors may require a more extended analysis, the overall expense is reduced because these cases are preselected.

TREATMENT

Management of cancers of the oropharynx is very challenging, given the essential role this anatomic site plays in breathing, speech, and swallowing. Alterations in any of these functions can significantly impact quality of life. Therefore, the goal of treatment is to not only achieve an oncologic cure but also preserve the multimodal function of the oropharynx. Traditional surgical approaches to the oropharynx are associated with significant morbidity, which prompted a shift toward nonsurgical modalities in the 1990s,

specifically using radiation or chemoradiation, which have been the mainstay therapeutic approaches for the past 15 to 20 years. Although the oncologic results for radiation-based therapies have been shown to be equivalent to traditional surgical approaches, the short-term and long-term sequelae can significantly impact quality of life.[63,64] However, recent technological innovations have led to a renewed enthusiasm for surgical options in the oropharynx through a transoral approach. These transoral approaches potentially allow for the adjuvant therapy to be modified based on the pathological findings of the resection specimen. This novel paradigm can reduce the radiation doses and may theoretically decrease the long-term side effects. These advantages become more imperative considering the large emerging population of young patients with HPV-related cancer who are expected to survive for many years.

Surgical Techniques

Open Surgical Approaches

Lateral and Suprahyoid Pharyngotomy.

The lateral pharyngotomy, originally described by Trotter in 1920, requires resection of the mandible, hypoglossal nerve, and lingual artery in order to achieve adequate visualization of the resection margins. Since that time, the technique has been modified in an effort to preserve these vital structures. The modern lateral pharyngotomy begins with a selective neck dissection of levels I–IV. After the specimen is removed, the lateral horn of the hyoid bone, superior laryngeal nerve, hypoglossal nerve, branches of the external carotid artery including the facial, lingual, and superior thyroid arteries are identified and preserved. The tendon of the digastric muscle is then divided exposing the stylohyoid and mylohyoid muscles, which are subsequently released from the hyoid at their insertion. The hypoglossal nerve and lingual artery, the two most important structures, are then isolated. At this point, the extent of parapharyngeal space involvement can be accurately assessed, and the ascending pharyngeal artery can be identified and ligated to allow the posterior belly of the digastric muscle, the stylohyoid muscle, and external carotid artery system to be retracted and rotated. This maneuver provides optimal exposure for entry into the pharynx. The point of entry into the pharynx is determined by the location of the tumor and most frequently is at

the level of the vallecula. Alternatively, the pharyngotomy can be performed more superiorly in the oropharynx at the level of the tonsillar region, but this requires transection of the styloglossus muscle. If the tumor extends to the vallecula, a third entry point is at the ipsilateral piriform sinus. Once the pharyngotomy is performed, the incised mucosa is retracted superiorly to allow adequate visualization of the lesion and circumferential margins, and the cancer is resected en bloc. For smaller defects, mobilization of the posterior wall of the pharynx from the prevertebral fascia can facilitate primary closure. In the cases of larger defects, a microvascular free tissue transfer is the preferred method for anatomic restoration for optimal speech and swallowing outcomes.[65]

Contraindications to this surgical approach include cancer arising from the vallecula, posterior pharyngeal wall, lateral epilarynx, nasopharynx, piriform sinus, or soft palate extending to lateral oropharynx. Additionally, extensive involvement of the parapharyngeal space, invasion of the nasopharynx, or involvement of more than half of the base of the tongue are considered contraindications.[65]

Similar to the lateral oropharyngotomy approach, the suprahyoid approach to the base of tongue has not gained significant popularity because of concerns raised throughout the 1900s that these approaches were oncologically unsound due to poor exposure and violation of the preepiglottic space.[66–68] More recently, the utility of the suprahyoid approach for T1 and T2 lesions has been confirmed, with favorable functional and oncologic outcomes.[69] The surgical approach begins with ipsilateral or bilateral neck dissections depending on the nodal status and the location of the primary. Once the neck dissection is completed, the suprahyoid muscles are transected 5 mm above the hyoid bone. Preserving this cuff of muscle facilitates the closure of the pharynx. The hypoglossal nerves are identified near the greater cornu of the hyoid bilaterally and preserved along with the superior laryngeal nerves and the lingual arteries. The preepiglottic space is then identified, and dissection is carried down to the vallecula. The pharyngotomy is facilitated by placing a retractor through the mouth into the vallecula, and the pharynx is entered at this level through the vallecula. The mucosal edge is retracted superiorly to allow visualization of the base of the tongue and the cancer. Under direct visualization, the specimen is removed with adequate margins. In most cases, the wound can be closed primarily by suturing the mucosa of

the base of the tongue to the vallecula. The remaining wound is closed in layers by reapproximating the musculature of the base of the tongue to the periosteum of the hyoid and the suprahyoid musculature to the cuff of muscle left on the hyoid.[69] The multilevel closure prevents fistula formation and allows for resuspension of the larynx, which will facilitate rehabilitation from postoperative dysphagia.

Ideal lesions for this approach are those that are confined to the base of the tongue, although cancers that extend laterally can be addressed with combination of suprahyoid and lateral pharyngotomy approaches. Contraindications to this approach include extension of the cancer to the circumvallate papillae, as the defect would be difficult to close primarily and the exposure is poor, and involvement of the epiglottis or larynx, as laryngeal resection would also be required.[69]

Mandibulotomy.

Mandibulotomy with paralingual extension into the floor of mouth provides excellent exposure to the tonsillar fossa, soft palate, and the base of the tongue. The mandibulotomy can be performed either in the midline or paramedially, between the lateral incisor and canine tooth. Lateral mandibulotomy is not recommended because the dynamic forces on the mandible are not symmetric, and intermaxillary fixation may be necessary to maintain appropriate occlusion. Additionally, the lateral mandibulotomy site is routinely within the radiation fields, which may lead to problems with wound healing and potentially osteoradionecrosis. A paramedian mandibulotomy offers the advantages of a median mandibulotomy and avoids the transection of the genioglossus muscles.

The skin incision is made from the lower lip to the hyoid bone, and a curvilinear extension can be used to include a neck dissection. The skin, subcutaneous tissue, and lip musculature are incised until the mandible is exposed. The paramedian mandibulotomy is performed through the socket of the extracted lateral incisor juxtaposed to the canine, after the mandible is preplated. Following transection of the mandible, the two segments are retracted laterally, and the mucosal incisions are made in the floor of mouth. In order to facilitate closure, a 6- to 8-mm cuff of mucosa should be left attached to the lingual gingiva. The mucosal incision can be extended to the retromolar trigone or into the vallecula if exposure to the base of the tongue

is necessary. The genioglossus muscles are preserved by dividing the mylohyoid muscle, and the lingual nerve permits the lateral swing of the mandible. Additional exposure to the base of the tongue can be achieved dividing the pharyngeal constrictors at the junction of the base of the tongue and the lateral pharyngeal wall. After the tumor is resected and the defect is reconstructed, the mandibular segments are approximated and replated with reconstruction plates, and the mylohyoid muscle and floor of mouth mucosa are closed in layers.[70]

A segmental mandibulectomy may be necessary when the mandible is directly involved with cancer or in the setting of recurrent cancer after radiation therapy where the vascular integrity of the periosteum is compromised. The exposure for a mandibulectomy is identical to the approach for the mandibulotomy. The extent of mandible to be resected is dictated by the extent of the cancer, but frequently the condyle can be preserved and the ascending ramus is divided at the level of the sigmoid notch.[70] Preservation of the condyle facilitates the reconstruction because a fibular osseous cutaneous free flap can be fixated to this residual fragment and maintains appropriate articulation of the temporomandibular joint. Alternatively, when only the ascending ramus or posterior aspect of the body of the mandible requires resection, a soft tissue reconstruction may be used with excellent cosmetic and functional outcome especially in edentulous patients. When a mandibulectomy is required, it is important to have an appropriate preoperative assessment for immediate reconstruction. The decision to reconstruct with a fasciomyocutaneous or osseocutaneus free tissue transfer or a regional pedicled soft tissue flap must be individualized for each patient and surgical defect. Regardless of the reconstructive option selected, all of the potential reconstructive options should be discussed preoperatively with the patient.

Transoral Approaches.

The transoral approach for radical excision of tonsillar cancers was originally described by Huet in 1951.[71] This procedure begins with palpation to confirm that the involved tonsil region is mobile because fixation to the deep fascial layers is a contraindication to this technique. Once mobility is confirmed, the raphe between the superior constrictors and buccinator muscles is identified, and the overlying mucosa is incised. The incision is made superiorly along

the maxillary dentition and inferiorly at the level of the posterior floor of mouth. The tonsil is grasped and retracted medially, which also brings the superior constrictor muscle medially. This opens the submuscular plane, which includes the palatopharyngeus muscle, palatoglossus muscle, and superior constrictors as the deep margin of the oncologic specimen. The plane is further developed to the prevertebral fascia using blunt dissection. With the prevertebral fascia exposed, the internal carotid artery can be identified posterolaterally to the deflected posterior tonsillar pillar. The anterior tonsillar pillar is transected superiorly. The posterior tonsillar pillar is also transected posteriorly and separated from the posterior pharyngeal wall. The inferior extent of the resection is at the level of the tongue where the anterior tonsillar pillar is transected and followed along the glossopharyngeal fold. With strong retraction superiomedially, the inferior margin is visualized at which point the stylopharyngeus and styloglossus muscles are transected. The posterior pharyngeal incision is then connected with this inferior margin to complete the resection.[5,72]

Contraindications to the procedure include trismus, fixation of the tonsil to the lateral oropharyngeal wall, and invasion of the mandible. Each of these features suggests infiltration of the cancer into the masticator and/or parapharyngeal space or into the prevertebral fascia. In addition, cancers that extend outside of the tonsillar fossa and into the nasopharynx, glossopharyngeal fold, base of the tongue, vallecula, pharyngoepiglottic fold, and/or pyriform sinus are not optimal for traditional transoral approaches. Lastly, poor exposure of the oropharynx due to individual patient anatomic or dental considerations is also considered a major contraindication.[72]

Transoral Robotic Surgery.

TORS was first described by Hockstein et al.[5,73] In using the robot for excising cancer of the tonsil, the cancer is initially examined with the patient under general anesthesia, and the margins of the cancer are marked. The cancer is then exposed using either the FK or the Crowe Davis retractor. At this point, the robot is docked at a 30-degree angle at the level of the patient’s axilla. Using the zero-degree telescope and electrocautery, an incision is made at the pterygomandibular raphe, and the buccal mucosa is retracted medially. The constrictor muscles are elevated off the prevertebral fascia and the styloglossus, and stylopharyngeus are identified and transected to expose

the adipose tissue overlying the prevertebral fascia. The carotid artery is then identified deep to the prevertebral fascia. At this point, the inferior incision is made along the posterior floor of mouth into the base of the tongue. The vascular pedicle of the inferior tonsillar pole is well visualized, and the vessels are controlled with either endoscopic hemoclips or electrocautery. If the dissection includes the base of the tongue, the lingual nerve and subsequently the lingual artery are identified. The lingual artery should be controlled with hemoclips. Once the lingual artery is controlled, the dissection of the base of the tongue continues down to the level of the vallecula. The specimen is now mobilized by resecting it away from the posterior pharyngeal wall.[74] Although the role of this surgical technique is still being determined, early oncologic results from several case series are comparable to the outcomes observed with radiation or concurrent chemoradiation (**Table 14.2**). However, many patients who undergo TORS also receive postoperative adjuvant radiation therapy or chemoradiation therapy, and therefore it is difficult to determine if TORS adds oncologic benefit or improved QOL in the patients with lesions amenable to TORS but with extensive primaries or regional nodal metastasis who will need adjuvant treatment.

Table 14.2 Oncologic Outcomes in Transoral Robotic Surgery

Study	No. of Patients	Post-Op XRT	Post-Op Chemo-XRT	Follow-Up (Months)	Locoregional Control	Overall Survival
Hurtuk et al.[75]	54	91%	63%	12	n/a	n/a
Genden et al.[76]	36	83%	46%	18	91%	90%
White et al.[77]	89	63%	48%	24	86%	89%
Weinstein et al.[78]	31	38%	38%	24	96%	100%
Weinstein et al.[79]	47	57%	57%	27	96%	96% (III)
						82% (IV)

Cancer-related contraindications for TORS include unresectable cervical lymphadenopathy, invasion of the mandible, pharyngeal wall or base of the tongue involvement requiring resection of >50% of these sites, radiologic evidence of involvement of the carotid artery, and fixation to the prevertebral fascia. The other limitation of transoral surgery is access, and therefore a thorough preoperative assessment of the patient and the characteristics of the cancer is essential. This assessment should include an evaluation of the dentition, presence of trismus or tori, size of the tongue, degree of neck

extension, sequelae of previous treatment, and the extent of the cancer. The oncologic outcomes for robotic surgery have been favorable thus far with overall and disease-free survival rates ranging from 82% to 100% and 86% to 96%, respectively (Table 14.2).

Transoral Laser Microsurgery.

Initially described by Vaughan, Strong, and Steiner in treating cancer of the larynx, this technique has been expanded to manage cancers of the oropharynx.[80,81] To adequately expose the primary cancer, a modified mouth gag or a modified expandable laryngoscope is used. Once exposure is achieved, an operating microscope or rod telescope is used to illuminate and magnify the operative field, which helps to identify healthy and neoplastic tissues at the perimeter of the resection. For exophytic cancers, the lesions are cored out and reduced in size, and the rind of cancer that remains is subsequently managed using a series of transtumoral incisions. The cancer is deliberately transected at a series of locations to map the deep extension along the invading front. A reasonable margin of 1 to 1.5 cm is excised beyond the invading front of the cancer. These margins are then inked to determine orientation and then analyzed by a pathologist. Frozen sections are used to direct further laser resection of residual microscopic or submucosal disease. Defects from these resections that expose the mandible or the great vessels of the neck or arefull thickness through the soft palate will require a soft tissue reconstruction using either local or free tissue flaps.[82] The oncologic outcomes for transoral laser microsurgery have been favorable thus far with overall and disease-free survival rates ranging from 82% to 100% and 86% to 96%, respectively (Table 14.2).

Radiation Therapy

Radiation therapy is a standard approach for definitive treatment for the oropharynx, which combines the goal of an oncological cure with organ preservation.[83] The current RT regimens are the results of several large randomized trials that have demonstrated favorable overall and disease-free survival rates,[84–89] although permanent dysphagia and gastrostomy tube usage rates remain substantial. Total radiation dosages and overall treatment times are regarded as important variables for oncologic response and for tissue toxicity. Therefore, alterations in fractionation schedules have been

investigated in an effort to improve locoregional control rates compared to conventional RT. Several studies have shown that altered fractionation improved the locoregional rate, and a meta-analysis of 15 trials demonstrated a survival advantage with altered fractionation regimens.[86,88,89] Because cancers of the oropharynx are adjacent to several critical structures, the ideal dose distributions would tightly conform to the target area and spare the nonaffected surrounding tissue. Traditional RT was restricted to lateral x-ray beams, which limited the ability to spare nearby unaffected tissue. Intensity-modulated radiation therapy (IMRT) allows for several treatment fields of nonuniform beam intensities, which generate more conformal dose distributions. One of the primary benefits of IMRT is the ability to conform the dose distributions around the cancer with relative sparing of the parotid glands, which has led to decreased xerostomia and improved functional and quality of life outcomes.[90,91] Although the benefits of IMRT are well established, there are tradeoffs with this technique. More specifically, the use of multiple oblique beams increases the volume of radiation, and therefore more tissues are being radiated, albeit at lower doses. The two regions that are associated with IMRT unique side effects are the far posterior structures, including the occipital scalp and brainstem, leading to increased occipital alopecia and nausea and vomiting, and at the anterior mandible, which correlates with oral cavity mucositis.[92] Additionally, IMRT has increased doses to the skin, larynx, and esophagus, which has some potential negative effects.

More recently, proton therapy has been implemented in the treatment of OPSCC. Protons confer advantages over more traditional forms of photon-based RT. IMRT uses photons (x-rays), which deposit the greatest radiation dose near the surface of the skin, and the dose slowly diminishes in intensity with increasing depth. In contrast, intensity-modulated proton therapy (IMPT) involves the use of protons, which deposit minimal dose near the surface of the skin but deliver most of the radiation dose to the tumor bed.[93]

Since 2011, radiation oncologists at the UTMD Anderson Cancer Center have treated 26 patients with OPSCC using IMPT, with a median follow-up time of 10 months (range, 0 to 22 months). Of the patients treated, 50% had never smoked and all had HPV-positive tumors. Systemic therapy was a component of treatment for 20 patients (77%), and the prescribed radiation dose was 70 Gy in 33 fractions. During treatment, five patients (19%)

developed grade 3 dysphagia requiring a gastrostomy tube, which is less than half the recently published rate for IMRT.[94] At last follow-up, all patients were disease free. Based on these encouraging preliminary findings of reduced toxicity and consistent disease response with IMPT, a phase II/III randomized trial comparing the toxicities of IMPT versus IMRT for advanced-stage OPC has been initiated.

Chemotherapy

Neoadjuvant Treatment.

Induction chemotherapy (neoadjuvant) in locally advanced cancer of the head and neck offers several theoretical benefits including the administration of more intensified chemotherapy than with concurrent therapy, with a potential for reducing the risk of distant metastases by treatment of micrometastatic disease.[63,95] Additionally, it can be used to reduce tumor bulk before a definitive approach to therapy and has been used to select patients for organ preservation. Despite these advantages, clinical trial data have not definitively demonstrated a survival benefit for induction chemotherapy, and its use remains controversial. Initial studies of induction chemotherapy showed improvement in locoregional control and overall survival and decreased development of distant metastases.[96,97] Unfortunately, a large meta-analysis that summarized the experience with induction chemotherapy demonstrated that only a 2.4% improvement in survival was offered by induction treatment, an effect that is inferior to the absolute survival benefit seen with concurrent chemoradiation therapy.[98] Iteractive analysis of these data revealed that platinum/fluoruracil (PF)-based induction regimens were associated with a 4.3% reduction in the rate of distant metastases.[99] In an effort to enhance the effect of the platinum/fluorouracil-based regimens, docetaxel was added as a third agent. The addition of docetaxel to PF resulted in a significant improvement in overall survival (71 vs. 40 months, $p = 0.0006$) compared to PF alone, but the rate of distant metastatic disease was not significantly different between the groups.[100] Although the addition of docetaxel to PF is a superior induction regimen than PF alone, the optimal concurrent treatment has not been identified, and the superiority of induction versus concurrent chemoradiation has not been demonstrated. Furthermore, HPV-related cancers have been shown to have high survival rates when

treated with induction chemotherapy, but it remains to be determined whether HPV status can be used as a predictive biomarker of response to treatment. In summary, to date, no trials have shown a clear survival benefit for induction chemotherapy over concurrent chemoradiation. Because of this, concurrent chemoradiation with cisplatin is still considered the standard of care for most patients with locally advanced SCC of the head and neck. As locoregional treatment continues to improve, distant metastatic failure is becoming a more frequent cause of disease-related death. Although induction chemotherapy could reduce this risk, the patients who would derive the greatest benefit remain largely unknown.

Concurrent Chemoradiation.

The classic pattern of relapse after RT in OPSCC has been local–regional recurrence, which has been attributed to the development of radioresistant cancer cells that persist after treatment. To overcome this resistance, chemotherapy has been added to sensitize the cancer cells to the damaging effects of ionizing radiation. For patients with locally advanced oropharyngeal cancer, a pivotal randomized phase III trial by the French GORTEC group revealed an improvement in both progression-free survival and overall survival for patients receiving combined modality therapy (42% and 51%) versus radiation therapy alone (20% and 31%) and improvement in locoregional control rates in the chemoradiation arm (66%) versus radiation therapy alone (42%) (**Fig. 14.8**). Despite these benefits, similar rates of distant metastases were observed in both arms (11%), and more significant side effects, including hematologic toxicities and grade 3 and 4 mucositis, were observed in the chemotherapy arm.[101] These toxicities led to a higher rate of temporary gastrostomy tube usage in the combination arm compared to the radiation therapy–alone arm. Taken together, these results suggest that the addition of chemotherapy concurrently to radiation therapy improves locoregional control, which translates into both an overall and progression-free survival benefit for these patients, at the expense of more acute toxicities.

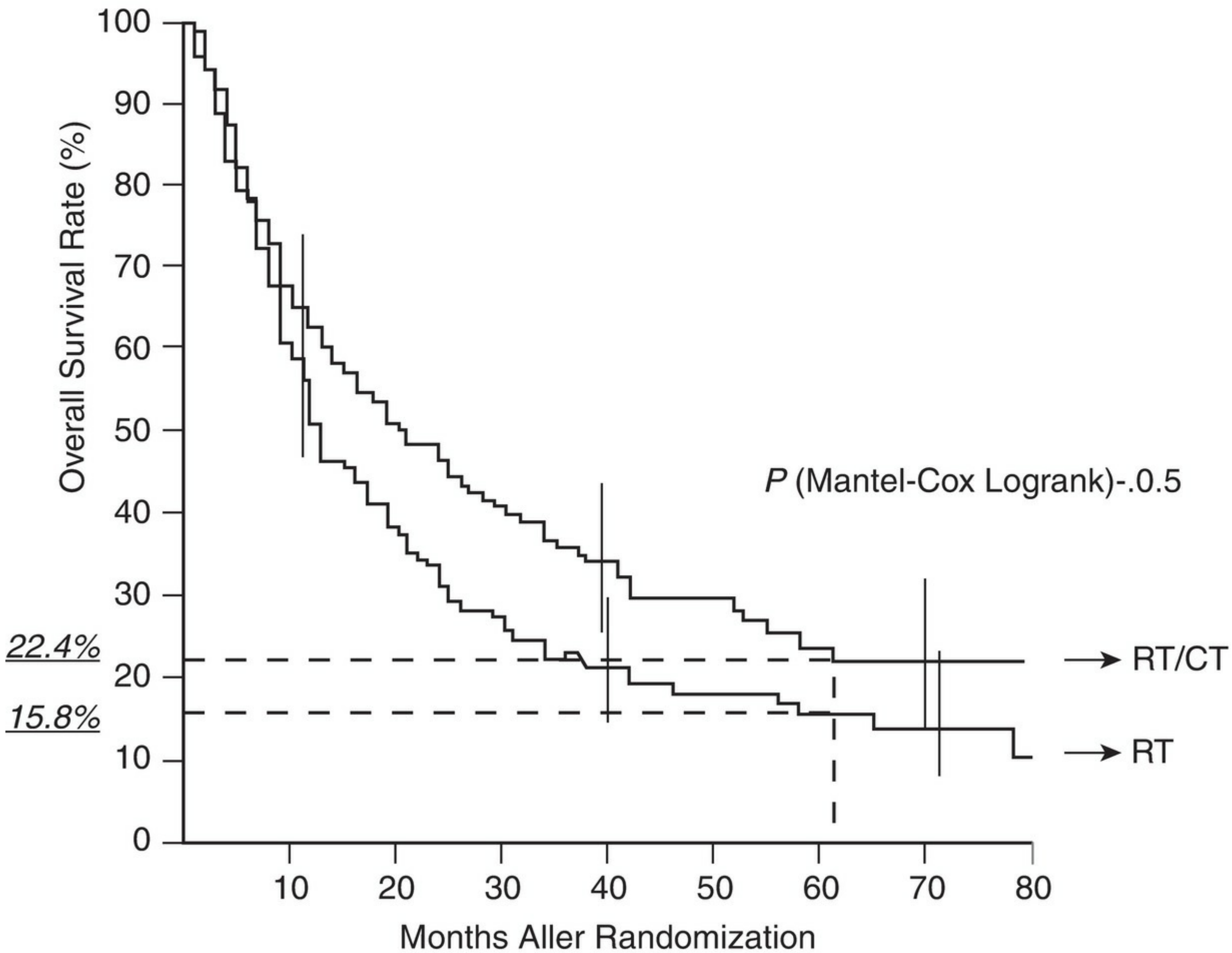

Figure 14.8. Overall survival among patients with cancer of the oropharynx treated with radiation therapy (RT) or with radiation therapy with concomitant chemotherapy (RT/CT) as analyzed by Kaplan-Meier method. (From Denis F, et al. Final results of the 94-01 French Head and Neck Oncology and Radiation therapy Group randomized trial comparing radiation therapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol.* 2004;22(1):69–76, with permission.)

To assess the benefit of concurrent chemotherapy for patients with either resectable or unresectable head and neck cancer, a meta-analysis of 87 randomized trials between 1965 and 2000 was performed. This analysis showed that the addition of chemotherapy led to an 9.3% reduction in locoregional recurrence at 5 years but the improvement in survival was modest, at only 5%.[99,101] The oncologic benefits of concurrent chemotherapy and radiation must be weighed against the associated increase in acute side effects with this treatment. For example, high-grade mucositis has been seen

in up to 71% of patients treated with concurrent therapy versus 39% in a radiation-only cohort.[87] In addition to cytotoxic chemotherapy agents, cetuximab, a monoclonal antibody inhibitor of EGFR, has been shown to improve locoregional control and overall survival relative by nearly 10% at 5 years to radiation alone (**Fig. 14.9**).[84] The role of cetuximab with radiation therapy for HPV-positive OPSCC, in place of cisplatin, is currently under investigation through a multi-institutional clinical trial.

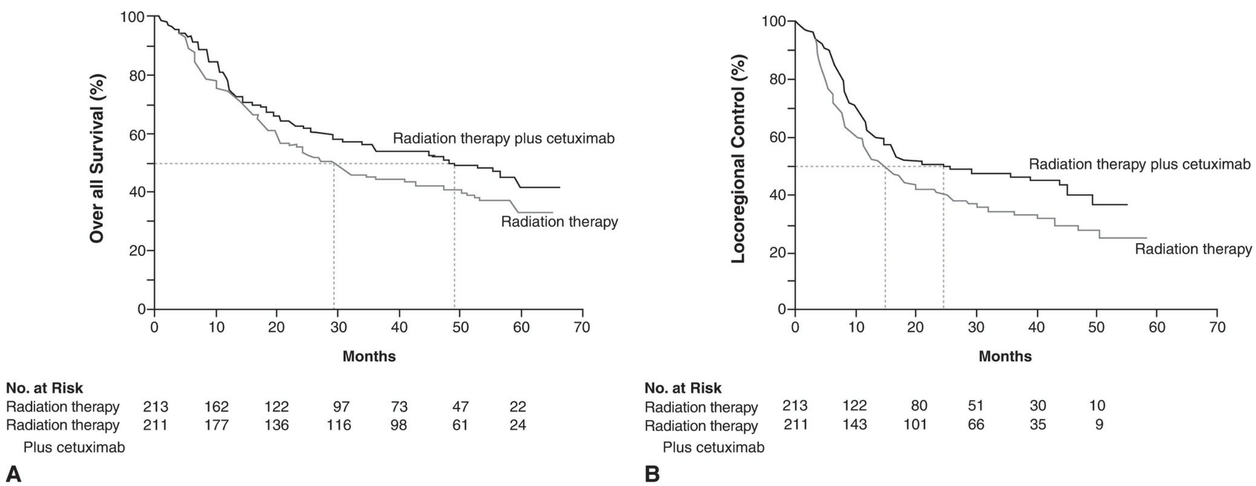

Figure 14.9. Kaplan-Meier estimates of overall survival (A) and locoregional control (B) among all patients randomly assigned to radiation therapy plus cetuximab or radiation therapy alone. (From Bonner JA, et al. Radiation therapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354(6):567–578.)

Adjuvant Chemotherapy.

The risk of recurrence for locally advanced OPSCC following surgical resection has traditionally been high. For patients with high-risk features, including perineural invasion, multiple positive metastatic nodes, and advanced T stage, postoperative radiation has been shown to decrease locoregional recurrences.[102] Furthermore, it has been shown that the addition of chemotherapy given concurrently can improve locoregional control rates in patients with high-risk features that include positive surgical margins, extracapsular extension, multiple positive lymph nodes, or perineural invasion.[103,104] There were conflicting results on an overall survival benefit between these two studies, which may have been due to the differences in

their inclusion criteria. A collaborative comparative analysis of these two trials identified positive surgical margins and extracapsular extension as the only two variables associated with improved outcomes with the addition of chemotherapy to radiation.[105] Thus, patients who undergo surgical resection of oropharyngeal cancer should be considered for adjuvant chemoradiation therapy when adverse pathological features are present. Whether this treatment paradigm is necessary for HPV-positive patients is currently under investigation.

Management of the Neck

In carefully selected cases of lateralized cancer of the tonsil, the treatment can often be restricted to the primary site and ipsilateral cervical and retropharyngeal lymph nodes. This management can be executed with surgery or definitive radiation. In the case of radiation, excellent locoregional control, low contralateral cervical lymph node failure rates, and a lower toxicity profile compared to bilateral neck treatment have been achieved.[106,107] Compared with bilateral neck irradiation, this approach substantially reduces the dose to the contralateral major salivary glands, uninvolved upper aerodigestive tract mucosa, and important swallowing structures.[108] The ideal patients for the unilateral approach had T2 or lower primary site disease with minimal soft palate involvement and no involvement of the base of the tongue. Locoregional control rates for both the primary site and ipsilateral neck were 100% at 5 years in this series of 102 patients, and at a median follow-up interval of 39 months, only 2 patients had developed a contralateral recurrence. With regard to toxicity, only 9 patients required placement of a feeding tube during therapy, and no patient experienced long-term dependence on a feeding tube.[108] With these promising findings observed with unilateral radiation therapy, the potential for unilateral surgical management of low-volume tonsillar cancer and the ipsilateral regional lymphatics as a single modality needs to be investigated.

Assessment of Treatment Response.

Following nonsurgical treatment of OPSCC, the primary site and neck should be clinically assessed 4 to 8 weeks following the completion of treatment. If persistent or progressive disease is detected, a CT and/or MRI with contrast should be obtained to assess the extent of local and regional disease.

Additionally, a CT scan of the chest or PET/CT should be considered for the evaluation of distant metastases disease. If a clinical response is detected 4 to 8 weeks after treatment, a CT and/or MRI should be obtained, and if there is no evidence of metastases, the patient can be observed with repeat imaging within 6 months. If persistent disease is detected, a PET/CT can be obtained 12 weeks from the completion of treatment or a neck dissection can be performed. If PET/CT is obtained, there are four treatment scenarios:

1. If no lymph nodes are detected or the lymph node is <1 cm but not FDG avid, then the patient can be observed with repeat imaging with 6 months.
2. If there is a lymph node <1 cm and FDG avid, then the patient can either be observed closely with repeat imaging in 4 to 8 weeks, undergo an ultrasound-guided fine needle aspiration, or proceed with a neck dissection.
3. If a lymph node is >1 cm but not FDG avid, then the patient can either be observed closely particularly if there has been significant nodal regression from pretreatment imaging, or an ultrasound-guided fine needle aspiration, or proceed with a neck dissection.
4. If a lymph node is >1 cm and FDG avid, then proceed with a neck dissection.

The addition of PET/CT imaging to the clinical evaluation of posttreatment surveillance of patients with OPSCC in the National Comprehensive Cancer Network Clinical Practice Guidelines is the result of several studies demonstrating the predictive value of this study. The negative predictive value for posttreatment PET/CT ranges from 85% to 99%.[109–116] Additionally, some studies have shown that patients with a negative first posttreatment PET/CT have an improved survival compared to those patients who have a positive PET/CT.[110–116]

Management of Local–Regional Recurrence

Despite the development of complex multimodality therapy for patients with OPSCC, 25% to 50% will recur.[117,118] Patients who develop recurrent OPSCC have long-term survival rates ranging from 23 to 35%.[119] Given the low survival rates and potentially high morbidity, multidisciplinary head and neck oncology teams must carefully weigh the risks versus benefits when considering treatment options. Although radiation therapy with or without

chemotherapy has become the preferred method of treating the majority of primary OPSCC, salvage options are limited for patients that have failed initial treatment.[120,121] Traditionally, salvage surgery has been considered the only potentially curative option, while chemotherapy and reirradiation have been reserved for unresectable disease or adjuvant therapy after salvage surgery.[122–126] Unfortunately, of the patients who recur, only 10% to 20% are favorable candidates for salvage surgery.[118,127] These patients are typically younger, have a longer disease-free interval after receiving definitive therapy, have small recurrent tumors where negative surgical margins can be achieved, and do not have recurrent neck disease.[118] Patients with recurrent disease harboring these characteristics and undergo salvage surgery with negative margins have an estimated 3- and 5-year overall survival of 42% and 28% respectively.[118] Given these low survival rates, it is important to consider all treatment options for recurrent OPSCC.

Reirradiation has been proposed as another curative approach for recurrent OPSCC with 5-year survival rates ranging from 13% to 22%, but it is associated with severe or fatal complications in 9% to 32% of patients.[128] Two Radiation Therapy Oncology Group trials evaluated reirradiation for recurrent head and neck SCC, which included 40% to 50% recurrent OPSCC. These trials reported greater than grade 4 acute toxicity in more the 25% of patients, treatment-related death in 8% of patients, and a median survival of 8 and 12 months, respectively.[129,130] In a retrospective review of patients with recurrent OPSCC, Zafereo et al.[118] reports a 5-year survival rate of 32% for patients who received definitive reirradiation or brachytherapy with or without chemotherapy.

Chemotherapy can be implemented as a palliative treatment but is not a curative option. Approximately one-third of patients with recurrent OPSCC have a partial response to platinum-based chemotherapy, with a median survival ranging from 4 to 6 months and 2-year overall survival rates of 5% to 10%.[119,131] Additionally, the addition of cetuximab to platinum–fluorouracil chemotherapy has shown a survival benefit compared to platinum–fluorouracil chemotherapy alone in patients with untreated recurrent or metastatic SCC.[132] Although a spectrum of treatment options is available for recurrent OPSCC, very few patients are able to achieve long-term survival; therefore, the successful management of the initial disease is crucial to improve outcomes for OPSCC.

BIOMARKERS AND RISK STRATIFICATION

Biomarkers aim to identify patients at high risk for recurrence and death from their disease (prognostic) and can also be used to predict patient response to specific therapies (predictive). Numerous studies have demonstrated that HPV-related oropharyngeal cancers are associated with improved outcomes.[3,133,134] Unfortunately, the presence of HPV alone is insufficient to stratify patients, and complementary biomarkers are now being identified to identify patients at highest risk for recurrence. To date, explored biomarkers include EGFR, p16, p53, Bcl-xL, and *p53* mutations. In a study of advanced OPSCC, patients with favorable expression profiles (low EGFR and high HPV titer/p16 or low p53 with low Bcl-xL) showed significantly improved overall and disease-free survival (**Fig. 14.10**).[133] Furthermore, a retrospective analysis of RTOG 0129 identified distinct risk categories for patients treated with concurrent chemotherapy and radiation based on HPV status, pack-years of smoking, along with the N stage for HPV-positive tumors and T stage for HPV-negative tumors. Using this stratification, low-risk patients defined as HPV-positive tumors and <10 pack-years of smoking and high-risk patients defined as HPV-negative tumors and >10 pack-year smoking history had 3-year overall survival rates of 93% and 46.2%, respectively. Intermediate-risk patients, with HPV-positive tumors with smoking history, had a 3-year overall survival of 70.8% (**Fig. 14.11**).[135] Bcl2 combined with HPV status has also been analyzed retrospectively and has identified a subset of patients at high risk for recurrence and more specifically for the development of distant metastases. Because high Bcl2 expression is associated with decreased survival outcomes, small molecule inhibitors are currently under investigation.[134]

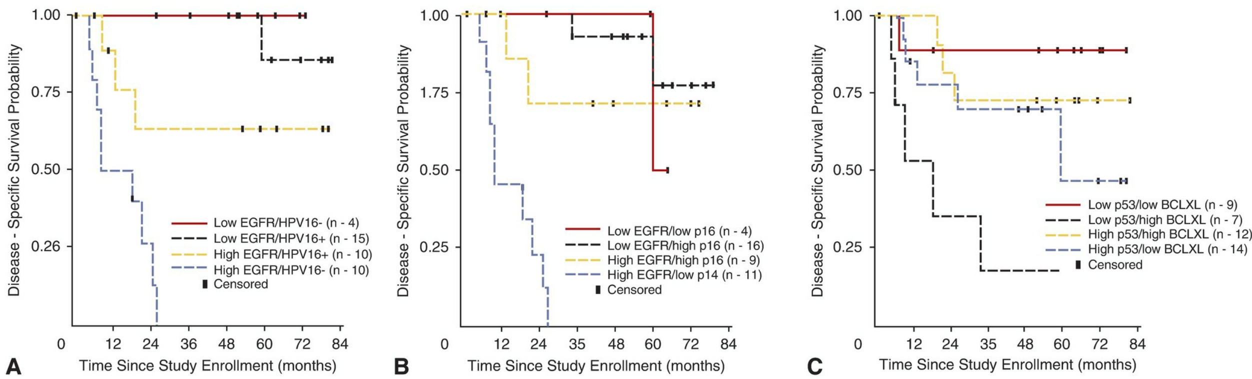

Figure 14.10. Kaplan-Meier curves for disease-free survival on risk stratification by EGFR, HPV-16, p16, p53, and Bcl-xL. **A.** Disease-specific survival according to epidermal growth factor receptor (EGFR) intensity and HPV16. **B.** Disease-specific survival according to EGFR intensity and p16 proportion. **C.** Disease-specific survival of patients on the basis of tumor p53 and Bcl-xL expression. (From Kumar B, et al. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. *J Clin Oncol*. 2008;26(19):3128–3137.)

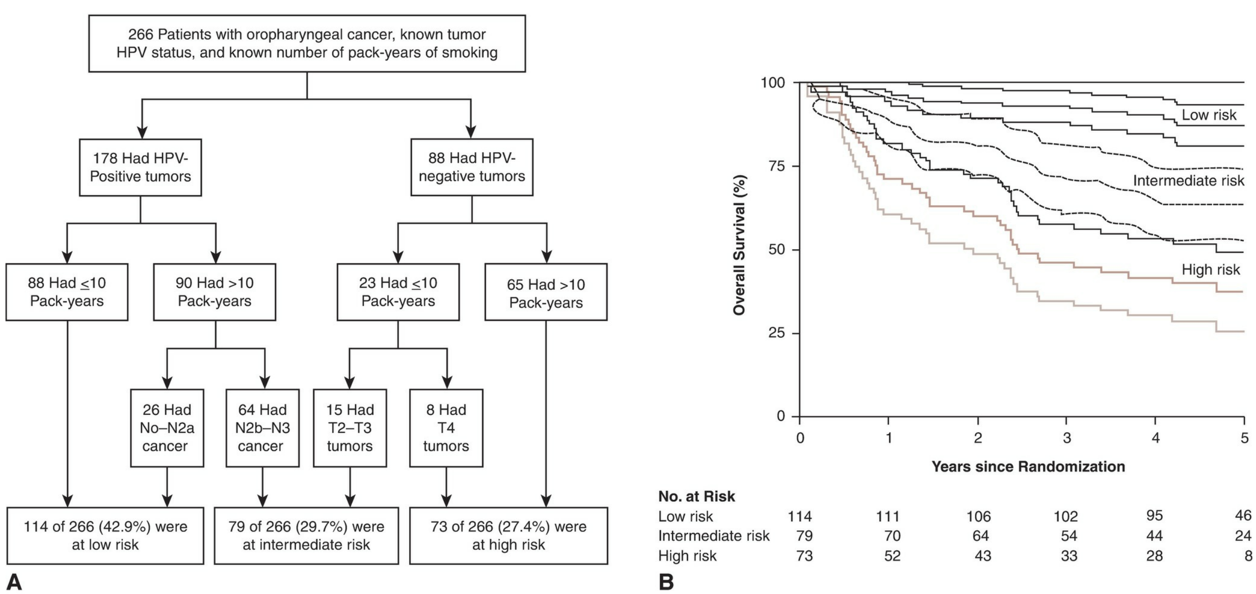

Figure 14.11. Risk classification scheme (**A**) and corresponding Kaplan-Meier curves for overall survival with their 95% confidence interval (**B**). (From Ang KK, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24–35.)

FUNCTIONAL OUTCOMES

Although swallowing outcomes highly depend on tumor burden, baseline functionality, treatment intensity, and supportive care, after primary radiation therapy or chemoradiation for OPSCC, it is estimated that on the whole, 7% to 31% develop chronic aspiration,[136,137] 11% develop aspiration pneumonia,[138] and are chronically feeding tube dependent.[139] To date, surgical series have been published in highly selected cohorts, and functional outcomes have been explored primarily with questionnaire data (rarely with instrumental studies). Acknowledging these limitations, after primary TORS for OPSCC, it is estimated that 0% develop chronic aspiration, 0% to 7% develop postoperative pneumonia, 20% to 40% require gastrostomy placement, and 0% to 7% are chronically feeding tube dependent after treatment.[140] Dose-dependent effects are robustly demonstrated with risk of dysphagia increasing after roughly 50-Gy mean dose to pharyngeal constrictors and 20-Gy mean dose to the larynx.[137]

Preventive swallow therapy is best practiced for patients receiving radiation therapy as a component of therapy for OPSCC and is supported by numerous randomized trials and large observational studies.[141–143] The central premise of proactive swallowing therapy is “Use It or Lose It” to mitigate muscular wasting and remodeling that occurs after even brief intervals of disuse. Preventive or proactive swallowing therapy encourages maximal use of the swallowing musculature during treatment by (1) avoiding NPO intervals, and (2) adhering to swallowing exercise regimes. To implement in the clinical setting, routine pretreatment referral to a speech pathologist is recommended.

SUMMARY

SCC of the oropharynx has classically been associated with tobacco and alcohol consumption. Unlike other aerodigestive tract subsites, the incidence of OPSCC has increased in recent decades due to increased infection with high-risk types of HPV. The integral role of the oropharynx in speech, swallowing, and breathing prompted a shift from the substantially morbid open surgical procedures toward nonsurgical organ preservation therapies. These radiation therapy-based approaches offer similar survival outcomes to surgery. Over the past two decades, numerous studies have attempted to determine the optimal regimen for head and neck squamous carcinoma, and

currently, the standard remains concurrent platinum-based chemotherapy with radiation. Yet, long-term dysphagia, gastrostomy tube usage, and osteoradionecrosis remain substantial survivorship issues for patients. The emergence of HPV-related OPSCC and novel surgical technologies has reignited an interest in surgical approaches to the oropharynx, and ongoing prospective clinical trials are exploring the oncologic and functional outcomes of TORS with radiation. Because HPV-related OPSCC is associated with improved survival outcomes, clinical trials are exploring whether low- and intermediate-risk patients can undergo treatment de-escalation, while achieving acceptable oncological outcomes. As the incidence of OPSCC continues to increase, the results from novel trials will hopefully provide evidence for the appropriate management of both low- and high-risk patients.

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15 Cancer of the Larynx

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The incidence of cancer of the larynx has stabilized at ~10,000 cases reported in the United States per year. The larynx is composed of three subsites that are unique in their predilection for regional spread, response to therapy, and capacity for laryngeal preservation with treatment. The major goals of therapy are to offer cure while preserving quality of life (QOL) and function. Posttreatment speech and swallowing capacity weigh heavily on a patient's selection from the variety of treatment options. With early-stage cancers, the monomodality treatment options of surgery or radiation offer the possibility of good locoregional control and maintenance of function. For advanced-stage lesions, the collaborative multimodality options of surgery with adjuvant radiation or primary chemoradiation (induction vs. concomitant) offer more aggressive approaches with associated toxicity and side effects while attempting organ preservation. As with all sites in the head and neck, recurrence has a poor associated overall prognosis and, when feasible, salvage options typically require radical surgical approaches with special techniques to facilitate functional rehabilitation.

Epidemiology

Approximately 0.7% of all new cancer cases and 0.6% of all cancer-related deaths are due to laryngeal cancer. It is the 21st most common cancer in the United States. The estimated 5-year relative survival for cancer of the larynx by stage at diagnosis, all stages included, was reported as 61% (for the years 2001–2007). The relative survival rate by race (all races included) for laryngeal cancer has remained stable over time with only a slight decline from 66% for 1975–1989 to 63% for 2001–2007.[1,2] In 2012, the American

Cancer Society reported 12,360 newly diagnosed cases of cancer of the larynx (male 9,840, female 2,520) and 3,650 deaths attributable to the disease.[1] In 2013, The SEER database estimated that 12,260 new cases of laryngeal cancer were diagnosed, representing 0.7% of all new cancer cases, with 3,630 attributable deaths.[2]

Statistics for patients with cancer of the larynx demonstrated a decrease in survival from the mid-1980s to the mid-1990s in a review performed by the National Cancer Data Base by Hoffman et al. It was noted that during this time frame, there was also an increase in nonsurgical approaches (chemoradiation or radiation alone) for the primary management of cancer of the larynx. This statistical decline in relative survival was most significant for patients with T1–T3 N0M0 supraglottic cancer.[3]

The male-to-female ratio is greater for glottic (9.2:1 among whites and 11.8:1 among blacks) than for supraglottic cancer (3–5:1 for both races).[4] Women are more likely to develop supraglottic cancer than glottic.[5] Cancer of the larynx has a peak incidence in the sixth and seventh decades with the median age at diagnosis of 65.[1] Less than 1% of cases occur in patients younger than 30 years of age, although it has been reported in children with no risk factors.[6,7]

Risk Factors

Multiple factors contribute to the development of cancer of the larynx. Foremost among them is the use of tobacco. Possible effects of secondhand smoking have not yet been carefully investigated for cancer of the larynx. The relationship of alcohol consumption to the relative risk is not clear; most studies show that it has a synergistic effect when combined with smoking. After controlling for factors such as tobacco exposure and average alcohol consumption, a case–control study using scoring with Michigan alcoholism and screening test (MAST) demonstrated an association between alcohol and the risk for development of glottic (OR = 1.9), supraglottic (OR = 2.3), and subglottic carcinoma (OR = 1.9). The highest risk was seen in patients consuming 42 or greater alcohol-based beverages per week (OR = 3.1).[8]

A review by the British Occupational Cancer Burden Study Group in

2012 attempted to summarize the occupational risk factors identified in Health and Safety Executive technical reports related to cancer of the larynx. Asbestos exposure and working within the rubber industry were considered to have a weak association with the development of cancer of the larynx. Contrary to this, occupational exposure to strong inorganic acids containing sulfuric acid was found to have a strong association (odds ratio = 2.90, 95% CI = 1.62 to 5.20) with cancer of the larynx and demonstrated an exposure–response relationship. The attributable fraction (AF) for all exposures combined for laryngeal carcinoma was 2.61% (95% CI = 0.83 to 4.32), largely due to the impact of strong inorganic acids, which equated to 20 attributable deaths.[9]

Dietary factors have also been postulated to have a significant influence on the development of laryngeal cancer. The International Head and Neck Cancer Epidemiology consortium investigated the impact of vitamin and mineral supplementation on the incidence of cancer of the head and neck by reviewing 12 case–control studies on the topic. The study included 1,329 patients with cancer of the larynx. Although supplementation with vitamin C (OR 0.76, 95% CI 0.59 to 0.96) and calcium (OR = 0.64, 95% CI 0.42 to 0.97) was associated with a reduced risk in the development of head and neck cancer (yet lacked a dose–response relationship), the authors ultimately failed to discern a strong association between the vitamin and/or mineral intake and risk reduction in the development of cancer.[10]

Reviews of the literature have failed to demonstrate a causal role of gastroesophageal reflux disease (GERD) as an independent risk factor in the development of cancer of the larynx. Cited confounding factors limiting the ability to confirm a statistical association include a coexisting history of habitual tobacco and alcohol use and the inherent inaccuracies in establishing the clinical diagnosis of GERD and laryngopharyngeal reflux (LPR).[11] Given that lower esophageal reflux is associated with the development esophageal adenocarcinoma and not esophageal squamous cell carcinoma, skepticism in the relationship of GERD and LPR to cancer of the larynx would appear reasonable.[12]

Given that chronic inflammation has been implicated as a potential etiology for the development of neoplasia, the question of whether anti-inflammatory therapy could be associated with a reduction in the risk of future development of specific cancers has provoked investigation. In a

nested case–control study, performed through the Seoul National University College of Medicine, the association between the use of inhaled corticosteroids and cancer of the lung and larynx was examined. Patients with a documented history of cancer of the larynx (*n* = 408) were matched with 1,651 controls. Although the authors noted a statistically significant reduction in the risk of developing lung cancer with the use of inhaled corticosteroids, there was no effect noted on the incidence of cancer of the larynx (positive or negative) with habitual use.[13]

The ARCAGE (alcohol-related cancers and genetic susceptibility) project was a multicenter case–control study performed in 10 European countries. As part of the study, investigators examined type-specific human papillomavirus (HPV) antibodies in 1,496 patients with an upper aerodigestive tract (UADT) cancer. The results of the study revealed only a marginal role for HPV6 (OR = 3.25, 95% CI+1.46 to 7.24 for HPV6 E7 seropositivity) in laryngeal cancer.[14]

A separate aspect of the ARCAGE study, examining the effect of medication and medical history on the development of UADT carcinomas demonstrated that the regular use of aspirin was associated with a reduced risk in the future development of cancer of the larynx (OR 0.74, 95% CI 0.54 to 1.01).[15]

Anatomy and Embryology

The larynx is divided into three anatomical subsites. Beyond the embryologic differences, the supraglottis, glottis, and subglottis have different lymphatic drainage pathways and therefore varied risk for regional metastasis in the setting of carcinoma. Clinically, neoplastic lesions in each of these subsites tend to present with a characteristic set of symptoms unique to the anatomic location of involvement.

Supraglottic Larynx

The supraglottis subunit includes the lingual and laryngeal surfaces of the epiglottis, the aryepiglottic folds, the arytenoid cartilages, the false vocal folds, and the ventricle. During embryologic development, these structures

are derived from the buccopharyngeal anlagen of branchial arches three and four. The glottic and subglottic subunits develop from the tracheobronchial anlagen of the fifth and sixth branchial arches. The embryonic fusion plane between the supraglottic subunit and the glottic and subglottic subunits is represented by a horizontal line drawn through the ventricle. This horizontal plane provides the anatomic and oncologic basis of supraglottic laryngectomy.

The supraglottic larynx is comprised of the suprahyoid epiglottis (both lingual and laryngeal surfaces), the infrahyoid epiglottis, the preepiglottic space, the laryngeal aspects of the aryepiglottic folds, the two arytenoids, and the ventricular bands (false cords). The inferior portion of the epiglottic cartilage is the petiole (**Fig. 15.1**). The inferior boundary of the supraglottis is a horizontal plane passing through the apex of the ventricle of the larynx. The supraglottis is intimately associated with the preepiglottic and paraglottic spaces, which can provide a pathway for transglottic spread (**Figs. 15.2 and 15.3**). The anatomic division is located at the arcuate line, which marks the change from respiratory to squamous epithelium and is reliably located at the apex of the ventricle. Thus, the roof of the ventricle is included in the supraglottis, and the floor belongs to the glottis.[16]

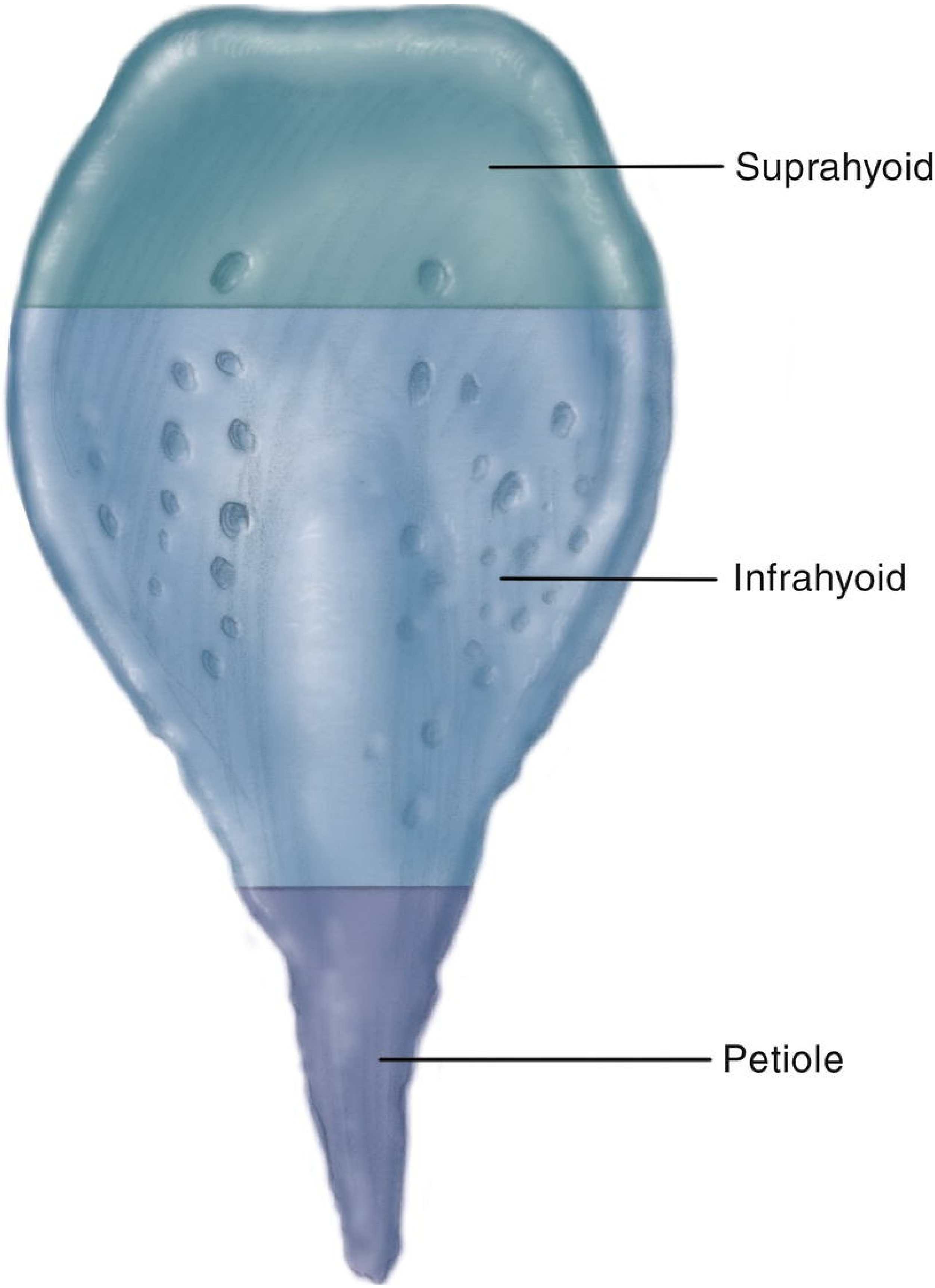
Suprahyoid
Infrahyoid
Petiole

Figure 15.1. The three portions of the epiglottis.

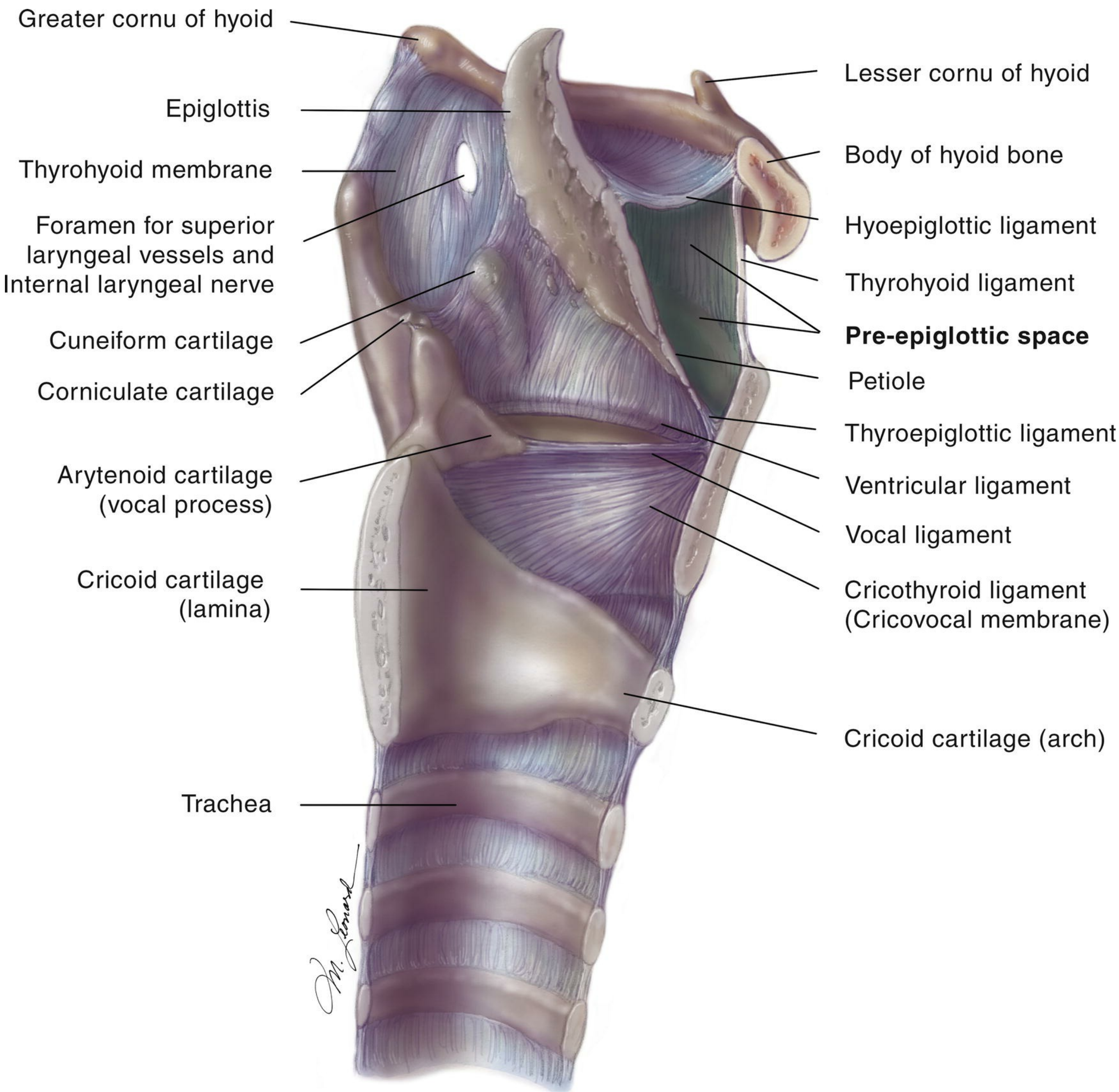

Figure 15.2. Sagittal cut of the larynx demonstrating the relative anatomy, highlighting the preepiglottic space.

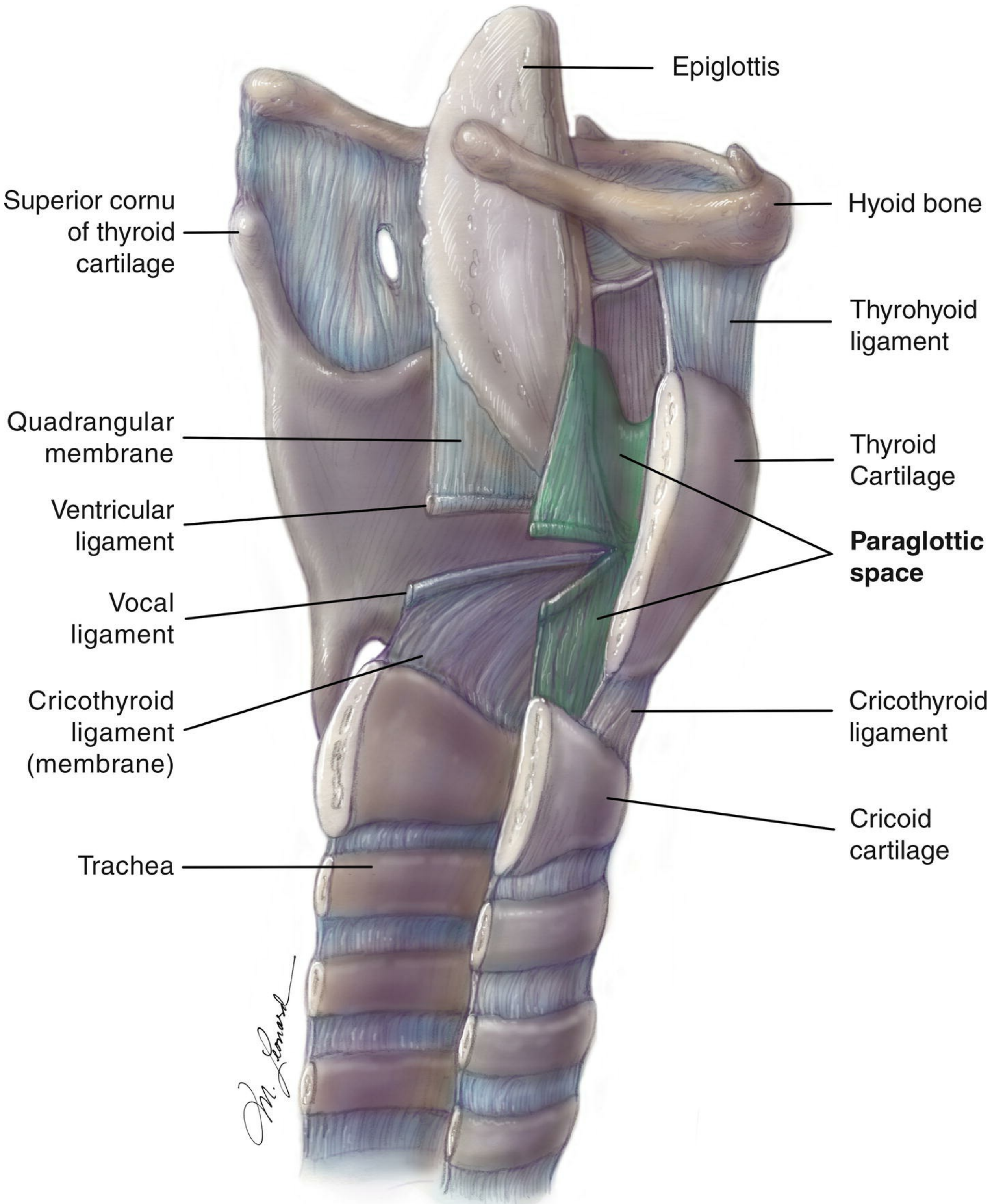

Figure 15.3. Sagittal cut of the larynx demonstrating the relative anatomy, highlighting the paraglottic space.

Histologically, the supraglottis is lined by ciliated columnar epithelium, as is

the majority of the upper respiratory tract. Exceptions are the free edges of the epiglottis and the aryepiglottic folds, which are lined with stratified squamous mucosa. Mucous glands are abundant and are of greatest density in the saccule and the periarytenoid areas. The predilection for lymphatic spread of supraglottic cancer is explained by the rich vascularity and lymphatics associated with this anatomic region.

Glottis

The glottic larynx includes the true vocal cords and the anterior and posterior commissures. The inferior border is the horizontal plane passing 1 cm below the apex of the ventricle. Histologically, the vocal cords are covered by stratified squamous epithelium around the edges and pseudostratified ciliated epithelium at the superior and inferior aspects, where the glottis merges with the supraglottis and the subglottis, respectively. The lamina propria has (1) a superficial layer composed of loose fibrous tissues that makes Reinke space and (2) intermediate and deep layers of elastic and collagenous fibers that form the vocal ligament. Blood vessels and lymphatics are almost absent in Reinke space, creating a resistance to the spread of early cancer of the glottis. No mucous glands are found on the free edge of the vocal cord, and only sparse glands are noted on the superior aspect. The conus elasticus extends upward from the superior border of the cricoid cartilage to merge with the inferior surface of the vocal ligament; it has the capacity to resist the extralaryngeal spread of glottic and subglottic cancer.

Subglottis

The subglottic larynx has no subsites and is the area of the larynx inferior to the glottis down to the inferior rim of the cricoid cartilage. It is a rare site of origin but is commonly involved by extension of glottic and supraglottic cancers. Cancer arising in the subglottis has a higher incidence of extralaryngeal spread owing to the proximity of the cricothyroid membrane and the rich postcricoid lymphatics.

Diagnosis

History, Physical Examination, and Laboratory Tests

Common presenting symptoms can include progressive hoarseness, chronic sore throat, referred otalgia, odynophagia, dysphagia, dyspnea, chronic cough, hemoptysis, and unexplained weight loss. Cancer in the glottis is seen in an earlier stage more frequently because of the notable finding of change in vocal quality not seen immediately with the other subsites. Patients with cancer of the supraglottis are more likely to present with advanced-stage cancer secondary to palpable regional metastases to the lymph nodes and a history of an ill-defined discomfort in the throat. The history should also assess for the current and prior use of tobacco products, average alcohol consumption, medical comorbidities (in particular chronic cardiovascular or pulmonary diagnoses), and potential occupational exposures.

A complete examination of the head and neck including detailed examination of the oral cavity, oropharynx, larynx, hypopharynx, and neck is critical. Indirect laryngoscopy (mirror examination) should be performed and supplements the findings of fiberoptic examination. Flexible fiberoptic laryngoscopy and/or videostroboscopy provide superior information about the anatomical and functional findings within the larynx and pharynx, which assist in treatment planning and staging. Careful palpation of the neck bilaterally is important with documentation of the location (group or level I to VI), size, mobility, and relationship of the node(s) to adjacent structures. Staging of the primary and the cervical lymph nodes is necessary prior to considering a patient's treatment options.

The diagnosis of a cancer of the larynx usually requires direct laryngoscopy and biopsy with the patient under general anesthesia. Direct laryngoscopy not only helps the clinician in making a diagnosis; it is also an important tool in proper mapping of the cancer for further management planning. Some authors advocate additional bronchoscopy and esophagoscopy in all patients with cancer of larynx for full pretreatment assessment and in evaluating for concurrent second cancers. Although the empiric performance of "panendoscopy" remains controversial, it is indicated when symptoms mandate additional evaluation. A typical example warranting this approach would be a patient who complains of dysphagia/odynophagia with supraglottic cancer spreading to the hypopharynx. Esophagoscopy would be performed to rule out extension to the cervical esophagus. For patients with enlarged lymph nodes in the setting

of a laryngeal cancer, fine-needle aspiration biopsy (preferably with ultrasound guidance) should be considered and can have a significant impact on staging and treatment.

Office-based transnasal flexible fiberoptic biopsy of laryngeal pathology has represented an alternative to conventional operative direct laryngoscopy with biopsy. Cohen et al. reported a low sensitivity of 69.2% with a specificity of 96.1% for office-based flexible fiberoptic laryngeal biopsy. Adequate tissue to establish the diagnosis of carcinoma was obtained in 35.4% of the 102 patients and allowed for early referral for treatment. The study's algorithm included follow-up operative biopsies for patients with initial benign or carcinoma in situ (CIS) biopsy results found with office-based biopsy. The authors expressed concern that pathologists were more reluctant to confirm a diagnosis of cancer with small tissue samples typically resulting from flexible fiberoptic office-based laryngeal biopsy.[17]

Laboratory testing at the time of initial assessment can be directed by the findings from the patient's history and physical examination. Preoperative pulmonary function testing should be considered along with history of activity level and exercise tolerance when making decisions about the suitability of a patient for partial laryngectomy. Consultations with other services, including radiation therapy, medical oncology, dentistry, speech pathology, psychiatry, and general medical services, are obtained as indicated.

Radiographic Examination

Clinical/endoscopic examination alone can fail to reveal extension of the cancer into the laryngeal cartilages and the extralaryngeal soft tissues. The combination of clinical/endoscopic and radiologic examination, by either computed tomography (CT) or magnetic resonance imaging (MRI), results in significantly improved staging accuracy (CT scan improves imaging in 80% of patients, and MRI in 87.5%). MRI is significantly more sensitive but is less specific than CT in detecting cartilage invasion. MRI can overestimate cartilage invasion and lead to overtreatment, whereas CT tends to underestimate cartilage invasion and may result in inadequate therapy.[18] A chest radiograph should be obtained to rule out concurrent cancer of the lung or metastatic disease.

Park et al. demonstrated that pretreatment Mean Tumor Volume (MTV) assessed by PET–CT correlated with 3-year LRC and OS for patients with locoregionally advanced laryngeal and hypopharyngeal carcinoma. The median SUVmax for patients was 10.3 and the MTV was 15 mL. MTV of >18 mL was seen to be a cutoff value that correlated with prognosis. The 3-year LRC and OS for patients with MTV ≤ 18 was 85.3 % and 91.4%, whereas for a MTV > 18, these values fell to 50.8% and 60.6%, respectively.[19]

The recommended timing of posttreatment PET–CT varies; however, most authors advocate that an accurate reading can be achieved at 10 to 12 weeks after CRT. However, it should be noted that a mild to moderate intensity of tracer uptake may persist for several months as a result of inflammation or radionecrosis and is typically diffuse and nonfocal. In addition, standardized uptake values (SUVs) cannot differentiate reliably between residual cancer and inflammation. Although SUV cutoffs have been reported to correlate with malignancy in a single institutional experience, these values have not been validated as reproducible at other institutions. The high NPV associated with PET–CT in the posttreatment setting is considered to be the most significant impact of this imaging modality on care.[20]

Staging

Primary Site

The specifics of the primary staging system for the supraglottic, glottic, and subglottic larynx are listed later in the discussion of the TNM staging system.

Metastases to Regional Lymph Nodes

The incidence and distribution of metastases to the cervical nodes from cancer of the larynx vary with the specific site of origin of the primary cancer and the stage of the primary cancer. The true vocal cords are nearly devoid of lymphatics so that early-stage glottic cancer rarely spreads to regional nodes. In contrast, the supraglottis has a rich and bilaterally interconnected lymphatic network. Advanced-stage glottic cancer may spread to adjacent soft tissues and to prelaryngeal, pretracheal, paralaryngeal, and paratracheal

nodes, in addition to upper, middle, and lower jugular nodes. Supraglottic cancer commonly spreads to upper and middle jugular nodes and only occasionally metastasizes to retropharyngeal nodes. Primary cancer of the subglottic spread initially to adjacent soft tissues and prelaryngeal, pretracheal, paralaryngeal, and paratracheal nodes and may metastasize to the middle and lower jugular nodes.

In clinical evaluation, the size of a mass in the neck should be measured and recorded in the medical record. It is recognized that most masses larger than 3 cm in diameter are not single nodes but multiple, confluent nodes with extracapsular spread. Clinically positive nodes are classified into three categories: N1, N2, and N3. In an N1 neck, the single enlarged lymph node is <3 cm in size. N2a represents a neck with a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension; N2b represents multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension; N2c represents bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension. Midline nodes are considered ipsilateral nodes. An N3 neck has a lymph node >6 cm in size and often represents unresectable cancer.

In addition to the components used to describe the N category, regional lymph nodes should be described according to the level of the neck involved. Imaging studies showing amorphous margins of involved nodes or involvement of internodal adipose tissue strongly suggest extracapsular (extranodal) spread of the cancer. No imaging study can yet identify microscopic foci in regional nodes. In addition, a distinction cannot be made between small reactive nodes and small malignant nodes unless central radiographic inhomogeneity is present.

Metastatic Sites

Distant metastases are more common among patients who have bulky (N2b, N2c, N3) lymph node metastases. Distant spread to the lungs is most common, whereas metastasis to the bone and/or liver occurs less often. Patients with extracapsular spread have a higher rate of metastasis to distant sites than those without extracapsular spread. Mediastinal lymph node metastases are considered distant metastases for the purposes of staging.

Staging

Clinical Staging

The larynx is assessed primarily by inspection, with the use of indirect mirror and direct endoscopic examinations. The cancer must be confirmed histologically, and any other data obtained by biopsy may be included. Cross-sectional imaging in laryngeal carcinoma is particularly recommended when the extent of the primary cancer is in question based on clinical examination. This may be accomplished with a high-resolution/fine-cut CT scan with contrast, through the larynx. In addition, it can help to distinguish between a coalescence of several lymph nodes and a single larger node, thereby making staging of the neck more precise. Endoscopic examination with the patient under general anesthesia is generally performed after completion of other diagnostic studies that accurately assess, document, and biopsy the cancer.

Pathologic Staging

All information used in clinical staging and in histologic study of the surgically resected specimen is also used for pathologic staging (**Table 15.1**). The pathologic description of any neck dissection should describe the size, number, and level of involved lymph nodes, as well as whether extracapsular spread is present. Specimens should also be examined for the presence of lymphovascular and/or perineural invasion in the primary cancer resection.

Table 15.1 Stage Grouping

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
IVB	Any T	N3	M0
IVC	Any T	Any N	M1

In a trial to assess for tumor biomarkers predictive of outcome in laryngeal carcinoma, Bradford et al. analyzed 58 pretreatment specimens as tissue microarrays with a panel of various biomarkers. Expression of Bcl-xL, a member of the antiapoptotic Bcl-2 family of proteins, was increased in patients with recurrent/persistent tumors. Overexpression of EGFR was correlated with an increase in risk of death from laryngeal carcinoma. When BAK (a proapoptotic protein) was expressed in low levels, cancers were more likely to respond to neoadjuvant chemotherapy. Lack of cyclin D1 expression and elevated cytoplasmic expression of CD24 were the best predictors of overall survival ($p \leq 0.05$) within the tested panel.[21]

In patients with advanced cancer of the larynx, individuals with high

circulating levels of CD4-positive T lymphocytes (both absolute count [$p = 0.006$] and percentage [$p = 0.04$]) demonstrated a better response to induction chemotherapy and experienced an improved survival. The results of these studies suggest that a peripheral blood draw could someday be used to identify patients with advanced-stage cancer that may be more likely to respond to an organ preservation protocol that uses induction chemotherapy (**Table 15.2**).[22]

Table 15.2 Definition of TNM

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
Supraglottis
T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumor invades mucosa of more than one subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of the base of the tongue, vallecula, medial wall pyriform sinus) without fixation of the larynx.
T3 Tumor limited to the larynx with fixation of the vocal cord and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space, and/or inner cortex of the thyroid cartilage
T4a Moderately advanced local cancer Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, and esophagus)
T4b Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis
T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis and/or occurs with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation and/or invasion of the paraglottic space and/or inner cortex of the thyroid cartilage
T4a Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (trachea, soft tissues of neck, including the deep extrinsic muscle of the tongue, thyroid, and esophagus)
T4b Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis
T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to the larynx with vocal cord fixation
T4a Moderately advanced local disease Tumor invades through the cricoid or thyroid cartilage and/or invades tissues beyond the larynx (trachea, soft tissues of neck, including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
T4b Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.
Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, larger than 3 cm and <6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral lymph node larger than 3 cm and <6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension
Distant Metastasis (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
Residual Tumor (R)
RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor
Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

From AJCC: Laryngeal. In: Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010:57–67.Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Natural Course of Disease

Nodal Metastases

Most lymph node metastases are found within levels II, III, and IV (**Fig. 15.4**). Levels I and V are rarely involved unless lymph node metastasis is extensive. Occult cervical lymph node metastases are often associated with cancer of the supraglottic larynx. Esposito et al. reported a rate of occult regional spread of 27% in 97 N0 patients with previously untreated supraglottic carcinoma undergoing neck dissection at the time of horizontal laryngectomy. In this group, based on the preoperative staging of the cancer, 14% of cases had occult metastases involving lymph nodes in T1 cancer, 21% in T2 cancer, 35% in T3 cancer, and 75% in T4 cancer. The incidence of occult metastases was higher for the less differentiated cancer and for primary cancer with a higher T stage. In a subset of patients with lateralized supraglottic primary tumors, contralateral occult regional spread occurs in 37% of patients. The authors stressed the importance of bilateral regional nodal treatment with supraglottic tumors even in the N0 setting.[23]

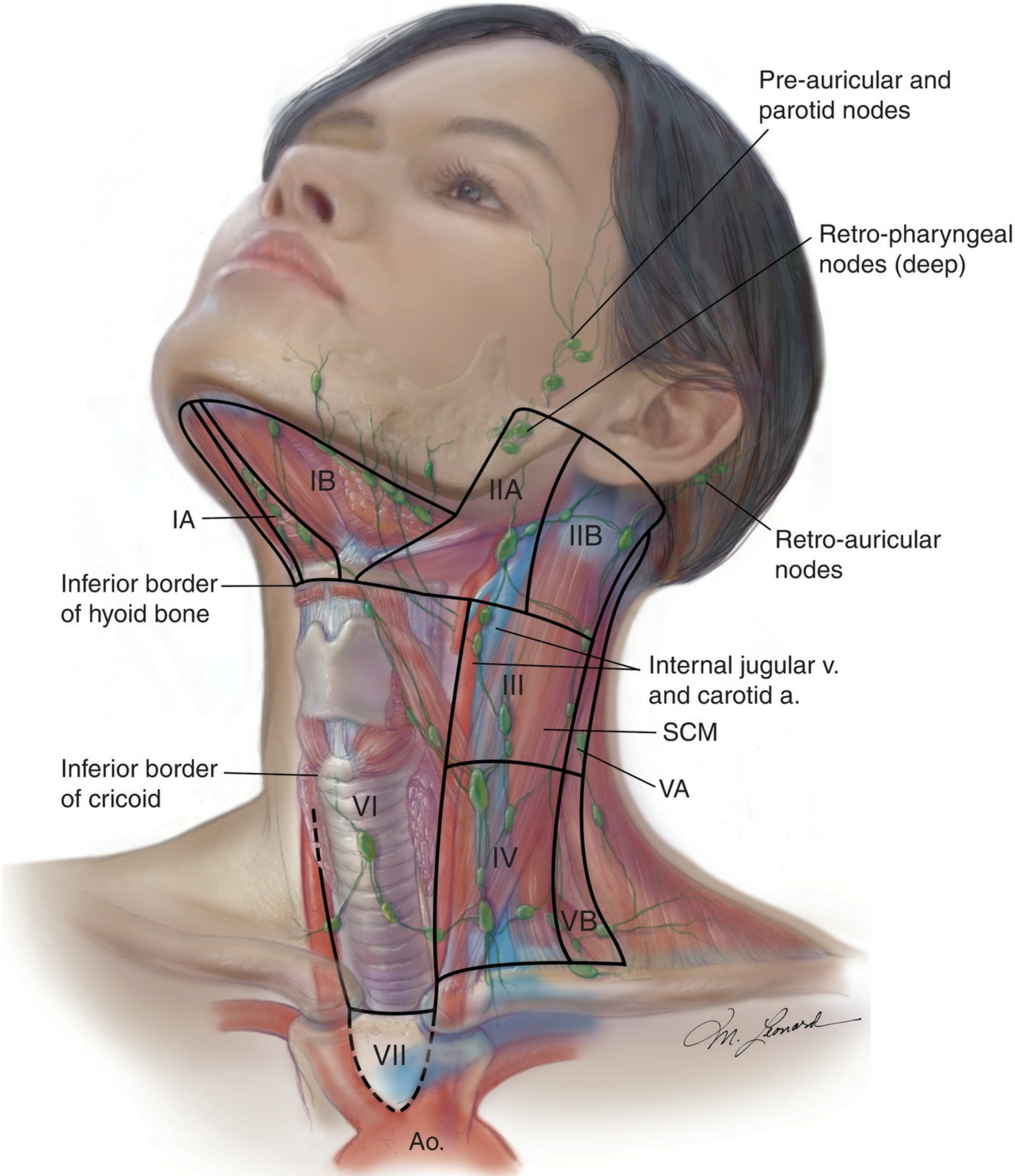

Figure 15.4. The lymph node levels of the neck.

In a study from Washington University of 2,550 patients with cancer of the larynx and hypopharynx, the overall incidence of delayed regional metastases was 12.4% (317/2,550 patients); distant metastases, 8.5% (217/2,550); and

second primary cancer, 8.9% (228/2,550). Delayed regional metastases and distant metastases were related to advanced primary cancer (T4 stage), lymph node metastases (node positive [N+]), the cancer arising in the hypopharynx as the primary site, and locoregional cancer recurrence ($p = 0.028$). Advanced regional metastases at initial diagnosis (N2 and N3 disease) increased the incidence of delayed and distant metastases threefold ($p = 0.017$). Incidences of delayed regional metastases by anatomic location of the primary cancer were glottic, 4.4%; supraglottic, 16%; subglottic, 11.5%; aryepiglottic fold, 21.9%; pyriform sinus, 31.1%; and posterior wall of the hypopharynx, 18.5%. Delayed regional metastases to the ipsilateral-treated neck had a significantly worse survival prognosis than did delayed metastases to the contralateral untreated neck.[24]

Distant Metastases

Distant metastases are associated with a poor prognosis. Among patients with cancers of the head and neck region, ~8% eventually develop distant metastases.[25] The lung is the most common site of distant metastases in primary cancer of the larynx. Staging has been helpful in predicting the likelihood of distant metastases with the highest frequency seen in patients in stages III and IV (85%). A supraglottic primary cancer is the most common subsite associated with the development of distant metastases.

The overall 5-year disease-specific survival after patients developed distant metastases was 6.4%. Distant metastases were related to advanced local cancer (T3 + T4), lymph node metastases at presentation (N+), and locoregional cancer recurrence ($p = 0.028$). A meta-analysis of variables that predispose to a higher incidence of distant metastasis identified tumor location (hypopharynx > larynx), advanced primary disease (T3 + T4), regional metastasis (N+), locoregional cancer recurrence, and advanced regional metastasis (N2 + N3).[26]

Second Primary Cancers

In a retrospective study from France including 410 patients, the incidence of second primary cancer was 23.9% (98/410). Cancer of the lung was the most common second primary and two-thirds of patients who developed a second primary cancer died of disease.[27]

In another retrospective review of 240 patients from Oregon with T1–T2 SCC of the larynx, 72% had glottic primaries, 27% had supraglottic cancer, and 1% had subglottic cancer. With a median follow-up of 68 months, 68 patients (28%) have developed 72 additional cancers. 15% were diagnosed with synchronous primaries.[28]

Pathology

Keratosis/Leukoplakia

Leukoplakia, also described as keratosis, of the larynx most commonly involves the true vocal cords and the interarytenoid area. It often occurs in smokers, singers, and professional voice users. Keratosis is grossly characterized as a white, thickened plaques. Microscopically, keratotic lesions are characterized by increased thickness of the normally present keratin layer of the epithelium. Hyperkeratosis is defined as the presence of a keratin layer in a normally nonkeratinized epithelium and may represent an early response to mucosal trauma.

Bartlett and colleagues performed real-time polymerase chain reaction analysis on the RNA of 17 specimens, originally classified clinically as glottic leukoplakia, yet subsequently diagnosed with nondysplastic keratosis, dysplasia, and invasive carcinoma on final pathology. Differential gene up-regulation and matrix metalloproteinase (MMP-1, MMP-2, MMP-9) expression was noted among the specimens suggesting a correlation between genetic changes and the progression of cancer. As a result of their findings, the authors suggest that the development of cDNA microarray genomic expression profiles could increase the sensitivity of assessment for patients with glottic leukoplakia by identifying disease progression reflected in markers of extracellular matrix degradation and the promotion of angiogenesis.[29]

Dysplasia

Dysplasia refers to a microscopic change that is characterized by cellular atypia, loss of maturity, and loss of stratification. Three grades of dysplasia are defined by the World Health Organization (WHO) classification[30]:

1. Mild—Changes are limited to the lower third of the epithelial thickness.
2. Moderate—Changes are limited to the lower two-thirds of the epithelial thickness.
3. Severe—Changes involve more than the lower two-thirds of the epithelial thickness. Cells are less crowded than with CIS and usually reveal greater differentiation.

Carcinoma in Situ

CIS may be present as the only lesion, or it may occur at the periphery of an invasive carcinoma. The standard criterion for diagnosis is the presence of atypical changes throughout the epithelium without evidence of surface maturation or invasion through the basement membrane.

Papillary CIS is a form of CIS characterized by papillary fronds with cytologic features of the classic CIS. The actual rate of malignant progression for untreated cases of laryngeal is unknown; however, some estimates have been reported to be as high as 40%. CIS of the larynx can be treated by means of biopsy, local excision, laryngofissure, stripping, or radiation.

Invasive Squamous Cell Carcinoma

Microscopically, more than 90% of cancers of the larynx are SCCs. They are graded into well-, moderately, and poorly differentiated cancers based on the degree of differentiation, cellular pleomorphism, and mitotic activity.

Persistence of SCC after radiation can be difficult to distinguish from postradiation atypia because of the similar histologic appearance. Immunoreactivity for keratin is universally present and cells also express epidermal growth factor receptors.

Various prognostic factors have been reported in the literature for invasive SCC and include clinical stage and site, histopathologic grade, lymphovascular invasion, perineural spread, lymph node spread (+/− extracapsular spread), HPV, tumor thickness/depth of invasion, and DNA ploidy.

Basaloid Squamous Cell Carcinoma

Basaloid SCC is characterized by a predominance of basaloid features in the

epithelium and is considered an aggressive variant of squamous cell carcinoma that can present in the larynx.

An association with HPV positivity and basaloid carcinoma has been seen with cancer of the oropharynx, yet similar findings have not been reported with laryngeal carcinoma.[31] Patients with laryngeal basaloid carcinoma typically present with a more advanced overall stage at diagnosis and have a worse disease-specific survival than individuals with conventional squamous cell carcinoma of the larynx. In a review of 145 cases of basaloid carcinoma of the larynx, 11.6% were found to harbor distant metastases at the time of initial presentation (vs. 2.7% for conventional squamous cell carcinoma of the larynx). The majority of basaloid carcinomas of the larynx present as supraglottic primaries (64.8%) and ~50% develop regional lymph node spread of metastases.[32]

Verrucous Carcinoma

Clinically, verrucous carcinoma is a slow-growing, locally aggressive cancer with an exophytic, fungating, warty, gray–white appearance and well-defined margins. Because it produces few early symptoms, patients often present with a bulky cancer. Histologically, this cancer is composed of elongated papillary fronds of well-differentiated squamous epithelium with extensive keratinization. Cytologic abnormalities are absent. The margins of the cancer have “pushing” rather than infiltrative growth that is usually accompanied by an exuberant host response of inflammatory cells. Regional lymph nodes may be enlarged and raise suspicion for occult malignancy, but this cancer does not metastasize, and nodal enlargement is invariably part of the host inflammatory response. The combination of the gross appearance of the cancer and the suggestive histologic findings is usually sufficient to establish the diagnosis.

Verrucous carcinoma constitutes from 1% to 3% of all cancers of the larynx. Within the larynx, a majority of these cancers arise from the glottis with the remainder diagnosed in the supraglottis. The typical patient is a male in his fifties or sixties who have been hoarse for at least a year before presentation. Smoking is a known risk factor. Overall prognosis is excellent with proper treatment, even among patients with locally advanced cancer. Fliss et al.[33] found 45% of patients with verrucous carcinoma of the larynx to have HPV detectable in their cancer by the polymerase chain reaction, all of

which cases of HPV were either type 16 or 18.

Huang et al. reviewed the experience of 62 patients with verrucous carcinoma of the larynx treated with primary radiation over a 43-year period. In the series, there were no reported episodes of posttreatment anaplastic transformation. Disease-specific survival was also noted to be comparable to those from series reporting on surgical management; however, local control (66% at 5 years) was noted to be inferior in comparison to surgery. Individuals who experienced a local recurrence (21/62) were capable of undergoing successful salvage resection of persistent cancer.[34]

Verrucous carcinoma of the larynx can be difficult to differentiate from benign papillary hyperplasia on biopsy if a limited quantity of tissue is available for histopathologic examination. Increased mean levels of expression of survivin, a member of the inhibitor of apoptosis protein family, in regions of parakeratosis have been shown to have the capacity to differentiate verrucous carcinoma from laryngeal papillary hyperplasia.[35]

Nonsquamous Tumors

Nonsquamous cancers account for <5% of all laryngeal malignancies. Among these, salivary gland tumors, cartilaginous neoplasms, sarcomas, and neuroendocrine carcinomas have been the types most commonly reported.

Adenocarcinoma

Adenocarcinomas of the larynx follow the distribution of the laryngeal mucous glands and are primarily supraglottic and subglottic in origin. Male predominance has been reported. Clinically, the cancers appear as submucosal, nonulcerated masses and symptoms are the same as for carcinomas of the larynx.

Most adenocarcinomas of the larynx present with advanced primary cancer and cervical lymph node metastases. Distant metastases to the liver and lung account for the dismal 5-year survival under 20%.[36] Secondary to the aggressive behavior of this primary, most authors have recommended radical surgery with total laryngectomy and bilateral neck dissections. Postoperative radiotherapy is usually advocated, although the numbers of reported cases are too small to know if this confers a survival benefit. Patients succumb to both locoregional failure and distant metastases.

Adenosquamous carcinoma is an uncommon but aggressive variant of head and neck squamous cell carcinoma with a propensity for regional and distant metastases with ~50% of cases presenting with a laryngeal primary. Very little has been reported concerning the risk factors or etiology of this variant. In a review by Masand et al. of 18 cases, 7 cases of primary laryngeal presentation were reported. The average age of patients was 58, all cases were male, and none of the cancers were positive for high-risk HPV.[37]

Adenoid Cystic Carcinoma

Although not exceedingly rare, a limited number of cases of adenoid cystic carcinoma have been reported and they are estimated to represent only 0.6% of all cancer of the larynx. The most common site of origin is the subglottis, followed by supraglottic primaries. These cancers produce only vague symptoms while they spread in a perineural and infiltrative growth pattern. When the primary originates from the subglottis, patients typically present with involvement of the laryngeal framework, trachea, thyroid gland, and esophagus. Metastases to the lung are common with this entity.

Adenoid cystic carcinoma of the larynx can be difficult to treat because of the predilection for perineural spread and pulmonary metastases. The mainstay of treatment, dependent upon stage and presentation, has typically been surgery (open vs. endoscopic approach) with potential adjuvant radiation therapy. Misiukiewicz et al. reported on the use of primary concomitant chemoradiation (CRT), using carboplatin and paclitaxel, as a means of organ-sparing therapy for patients who otherwise would have required laryngectomy and radiation. Locoregional control with functional laryngeal preservation was obtained with a follow-up of at least 5 years in two patients. The authors suggested that this regimen represented an alternative for selected patients with this diagnosis when laryngeal preservation is desired and salvage laryngectomy would be used for nonresponders.[38]

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma of the larynx is an uncommon cancer that typically presents in older males with the supraglottis as the most common primary site. The worst prognosis is seen with patients with high-grade

cancer. Low-grade cancers rarely spread beyond the confines of the larynx and conservation surgical approaches without neck dissection may be curative. Radiation has not been shown to be effective when used as a single modality.

The management of high-grade mucoepidermoid carcinoma is similar to that of SCC. The extent of surgery is dictated by the extent of the cancer and elective neck dissection is recommended, even for smaller cancers, because of the risk of occult neck metastases. Radiation therapy is usually administered in the adjuvant setting.[39]

The management of intermediate-grade cancer is controversial, and many authors tend to follow a more aggressive approach. Surgery is the mainstay of therapy. The use of postoperative radiation therapy varies according to the surgical margins and other factors, such as the patient's age and the presence of regional metastases.[40]

Chondrosarcoma

Chondrosarcoma is the most common sarcoma of the larynx. Its incidence is difficult to know because the low-grade form of this tumor is often confused with a benign chondroma. It predominantly affects men (3:1 male-to-female ratio) between the ages of 50 and 70 years and arises from the hyaline cartilages of the larynx.[39] The most common of these sites are the cricoid (especially the posterior lamina) (70%), the thyroid (20%), and the body of the arytenoid cartilage (10%).

Chondrosarcoma arising from the cricoid cartilage tends to grow into the airway and cause progressive obstruction, whereas chondrosarcoma arising from the thyroid cartilage typically protrudes laterally and presents as a firm mass in the neck. Endoscopically, the tumor appears as a firm, submucosal mass that is difficult to biopsy because it is so dense. On imaging, these lesions are typically hypodense, well-circumscribed masses containing mottled calcifications with smooth walls centered within the cartilage.[41]

The management of chondrosarcoma varies with the grade and extent of the tumor. The primary modality of treatment is surgery. For low-grade and some medium-grade tumors, local control is the goal. Partial laryngectomy with voice preservation and reoperation if the tumor recurs is an option in selected patients. Challenges arise with tumors arising in the cricoid, and a

variety of techniques have been described to reconstruct the larynx following partial resection with reconstruction of the cricoid, using hyoid bone, rib, and strap muscle. High-grade chondrosarcomas usually require a total laryngectomy, with neck dissection reserved for clinical or radiographic evidence of metastasis.

Five-year survival rates are not useful data for chondrosarcomas of the larynx, especially with low-grade tumors, because recurrences and subsequent mortality may occur well beyond this time point.[42]

Neuroendocrine Tumors

The second most common tumor type in the larynx takes rise from neuroendocrine family of neoplasms, which include carcinoid tumors (6.6%), atypical carcinoid tumors (53.7%), small cell neuroendocrine carcinomas (27.6%), and paragangliomas (12.1%).

Laryngeal carcinoid tumors can be mistaken as being an indolent pathology yet has reported rate of regional and distant metastasis of 33%. It typically presents in the supraglottic or transglottic lesion. Conservative surgical resection with therapeutic neck dissection (in N+ patients) has been advocated. Elective neck dissection is considered unnecessary because of the low rate of associated occult spread. Radiation is considered to be ineffective in the management of this pathology.

Atypical carcinoid tumors are aggressive lesions with regional and distant metastatic rates ranging from 43% to 67%. The reported 5-year survival is <50%. Histopathologic misclassification of atypical carcinoid as carcinoid tumor can occur and may prompt re-evaluation of tissue specimens if the clinical behavior of the tumor is uncharacteristic for a specific patient's presentation. Surgical resection is considered the treatment standard with bilateral elective neck dissection being advocated for supraglottic presentations. One series from MD Anderson reported on the use of radiation and chemotherapy (primary therapy and as an adjuvant) in the care of selected patients with mixed results.

Small cell neuroendocrine carcinoma has a poor associated prognosis with 90% of patients experiencing regional and/or distant metastasis. The 5-year survival is typically <10%. Paraneoplastic syndromes can occur in association with this diagnosis. Nonsurgical treatment is advocated for this

diagnosis and frequently requires a multidrug chemoradiation regimen.

Paraganglioma of the larynx is a benign tumor with a female predominance. Surgery is the treatment of choice for this lesion with both open and endoscopic CO_2 lesion resections described.[43]

Liposarcoma

Liposarcoma of the larynx is a rare entity that typically presents as a supraglottic lesion in males in the fourth to seventh decade of life. The tumors tend to be low grade and are rarely associated with regional or distant spread. The four most commonly described histologic variants are pleomorphic, round cell, myxoid, and well-differentiated liposarcoma. Well-differentiated liposarcoma represents ~65% of cases and can be easily confused with a basic lipoma both macroscopically and microscopically. Wide surgical excision is advocated for this tumor with little evidence of a role for radiation in this setting. Recurrence is common and occurs in over 50% of reported cases.[44]

Composite Tumors

Synchronous presentation of small cell carcinoma and squamous cell carcinoma of the larynx, also known as “composite tumor of the larynx,” is rare and represents a clinical quandary and requires a collaborative approach to management.[45] Additional reports of synchronous “double-tumor” presentations, such as with squamous cell carcinoma in the setting of laryngeal chondrosarcoma, have also been reported.[46]

Treatment of Cancer of the Larynx

Early-stage laryngeal carcinoma (stage I or II) is usually treated with a single-modality regimen involving surgery or radiation therapy. Although controversy exists regarding the relative merits of either treatment modality, the rates of cancer control are similar, and patients should be made aware of the options available. Surgical options include endoscopic laser resection, open partial laryngectomy, and total laryngectomy.

In contrast, advanced-stage cancers of the larynx typically require combined multimodality therapy to treat the primary site and regional lymphatics. Primary surgical management and adjuvant radiation therapy (with or without chemotherapy) versus chemoradiation with surgery reserved for salvage are typically the options employed in this setting.

Surgical Treatment

The options of conventional (open) conservation surgery (CCS), transoral endoscopic laser microsurgery (TLM), and supracricoid partial laryngectomy (SCPL) provide a variety of treatments that can offer the goal of cure with preservation of laryngeal function and integrity of the airway.

Although CCS has been supplanted for many early-stage lesions by TLM, centers throughout the world have reported favorable results with CCS, which may be modified to allow resection of more extensive tumors. A number of extended CCS procedures exist for the management of glottic cancer involving both vocal cords and the anterior commissure (AC), for cancer in the paraglottic space with vocal cord fixation, and for supraglottic tumors involving the glottis or hypopharynx.

TLM has proved to be an effective, minimally invasive, and functionally satisfactory procedure for management of selected T1 and T2 glottic cancers, as well as for T1–T3 supraglottic cancers (**Figs. 15.5 and 15.6**). The procedure may be effectively employed in combination with neck dissection and postoperative radiotherapy when necessary, particularly for moderately advanced supraglottic carcinomas.

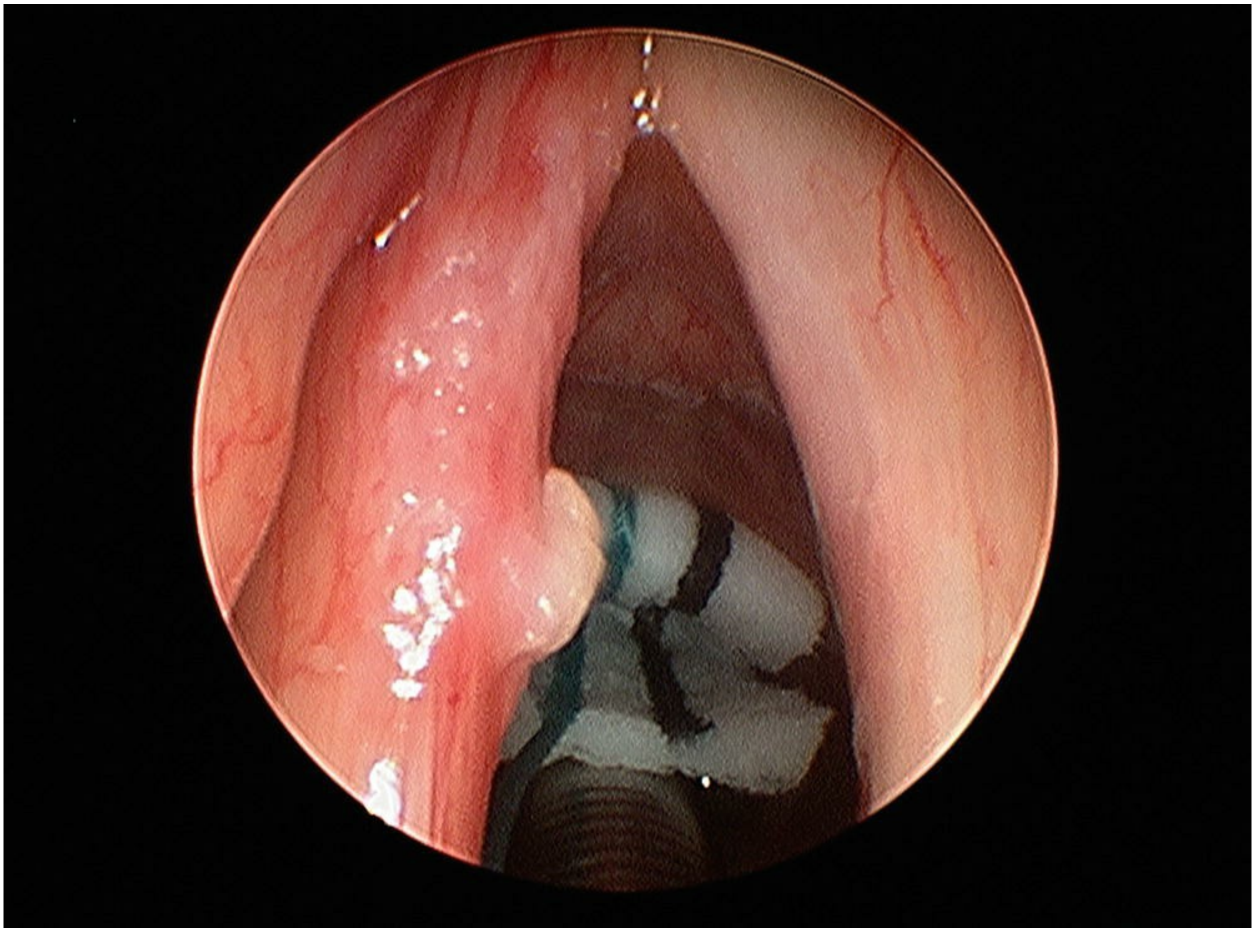

Figure 15.5. T1a glottic carcinoma prior to resection.

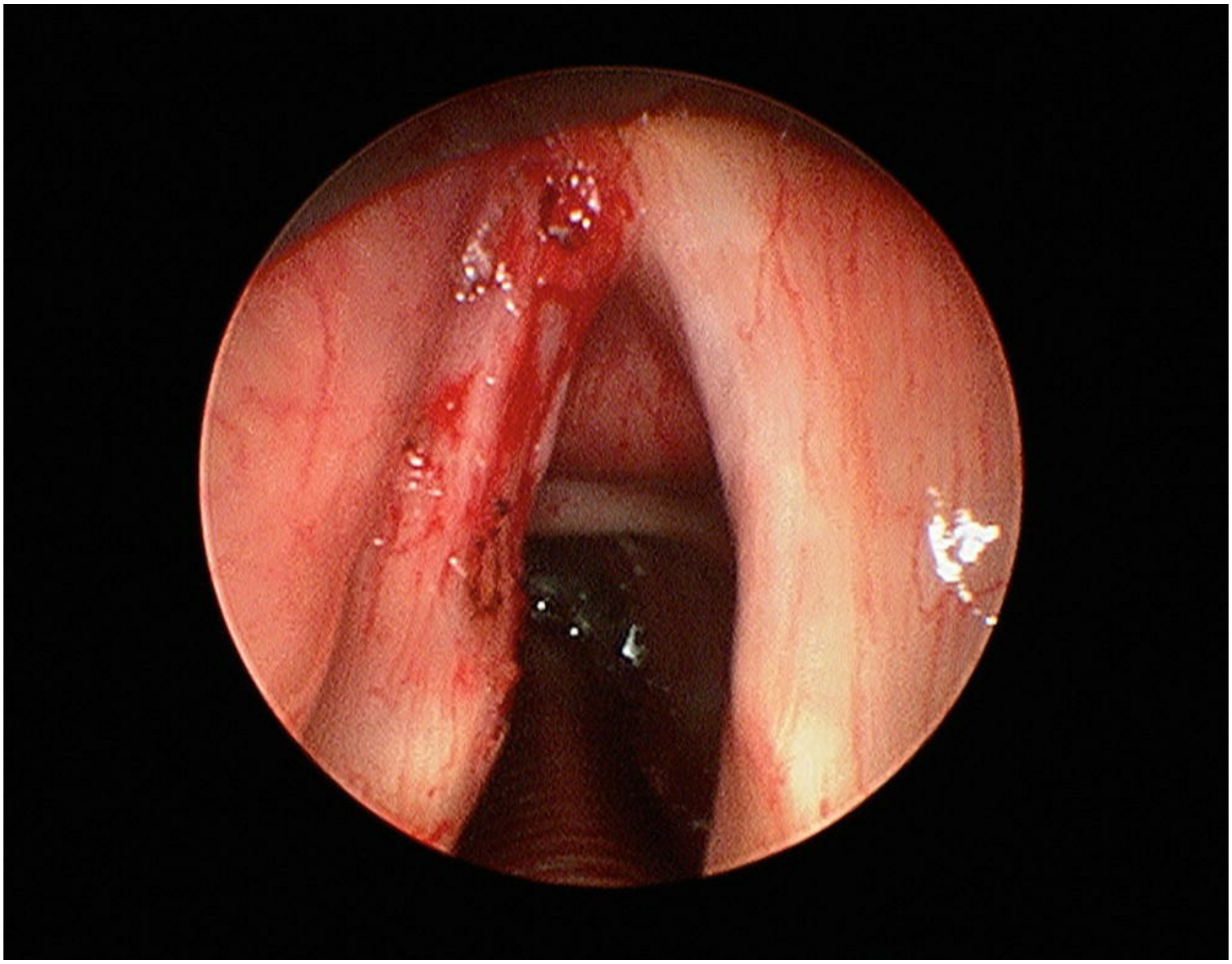

Figure 15.6. T1a glottic carcinoma after TLM (using CO_2 laser) resection of tumor potential paths of spread of tumor within the laryngeal ventricle.

SCPL has proved effective in the management of glottic and supraglottic cancers, even when involvement of the paraglottic space and the thyroid cartilage exists, provided at least one arytenoid unit could be preserved with clear margins. Invasion of the cricoid cartilage is the most significant limitation of this procedure. Voice quality results are variable.

All three surgical approaches have been employed for radiation failure but with increased failure and complication rates compared with primary surgical treatment. A decision to treat a cancer of the larynx initially with radiation may complicate the potential for a satisfactory result with salvage partial laryngectomy. The treatment of cancer of the larynx should be individualized with various treatment modalities and surgical procedures according to the size and extent of the cancer, the age and physical condition

of the patient, and the skill and experience of the treating physicians.

In 1866, Patrick Watson of Edinburgh performed the first laryngectomy. The patient was a 36-year-old man whose larynx was being destroyed by syphilis. He survived the operation but died several weeks later from pneumonia; after his death, the procedure was condemned. In 1873, Billroth of Vienna performed what is considered to be the first successful laryngectomy. Since then, surgery for cancer of the larynx has seen significant advances that have made the surgery both safe and reliable.[47]

Cancer of the Glottis

Endoscopic Resection

The European Laryngological Society proposed a classification of different laryngeal endoscopic cordectomies in order to ensure better definitions of postoperative results; the word *cordectomy* is used even for partial resections because it is the term most often used in the surgical literature. The classification includes eight types of cordectomies: (1) subepithelial cordectomy (type I), which is resection of the epithelium; (2) subligamental cordectomy (type II), which is resection of the epithelium, Reinke space, and the vocal ligament; (3) transmuscular cordectomy (type III), which proceeds through the vocalis muscle; (4) total cordectomy (type IV); (5) extended cordectomy that encompasses the contralateral vocal fold and the AC (type Va); (6) extended cordectomy that includes the arytenoid (type Vb); (7) extended cordectomy that encompasses the subglottis (type Vc); and (8) extended cordectomy that includes the ventricle (type Vd). These operations are classified according to the surgical approach used and the degree of resection. Each surgical procedure ensures that a specimen is available for histopathologic examination (**Fig. 15.7**).[48]

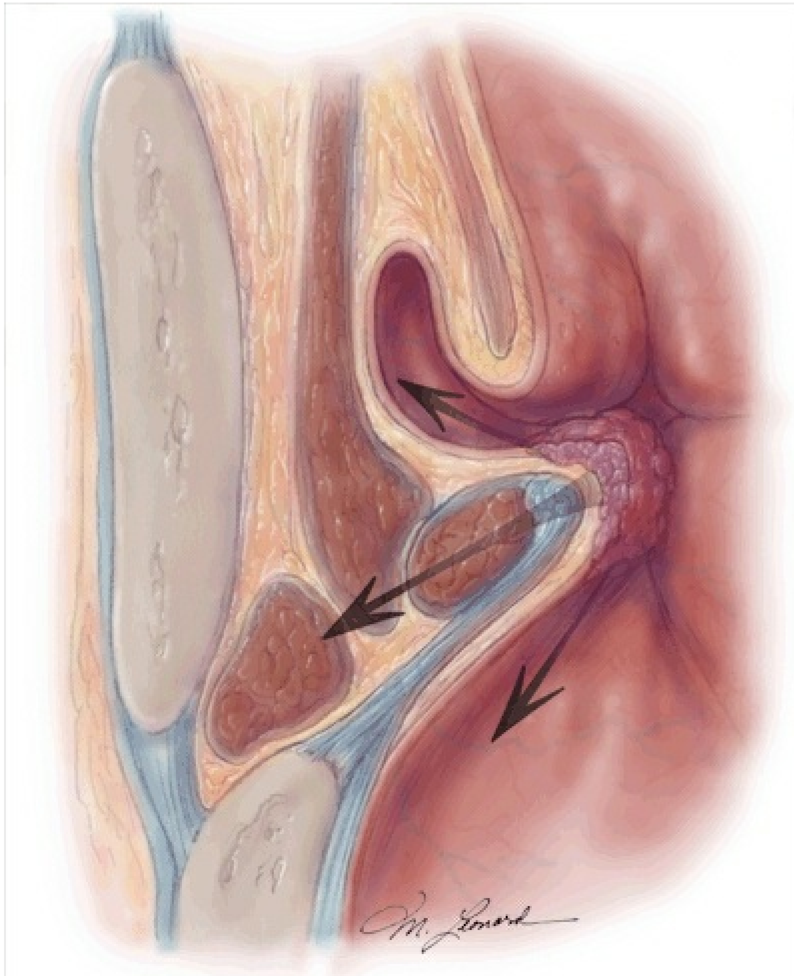

Figure 15.7. Path of potential lateral deep invasion for a primary cancer of the glottis that may affect the extent of endoscopic resection.

Hakeem et al. reviewed a group of 296 patients with early cancer of the glottis to evaluate the impact of AC involvement on disease control while using transoral endoscopic resection techniques. In the series, 61/296 had AC involvement. Negative margins were obtained at the original resection in 77.05% of patients with AC involvement versus 94.55 of the time without AC involvement. The local recurrence rate for patients with AC involvement was significantly greater than for those without involvement (29.51% vs. 18.35%, $p = 0.0001$). Of the patients with AC involvement and local recurrence, laryngeal preservation with open and endoscopic techniques or radiation therapy was possible in 68.85%. However, the laryngeal preservation rate (95.8% vs. 93.26%, $p = 0.287$) and overall survival were not affected by cancer involving the AC.[49]

Blanch et al. reviewed their experience in a series of 107 patients with transoral endoscopic CO_2 laser resection of T2/T3 glottic carcinomas with AC involvement. Tumor recurrence was statistically related to the margin status at original resection ($p = 0.01$) and the experience of the surgeon ($p = 0.02$) but was unrelated to T stage. The experience of the surgeon reflected a comparison of the first 5 years (1998–2003) in which transoral laser microsurgery was performed in the author’s department versus the subsequent 5 years (2003–2008). They reported 5-year overall and laryngectomy-free survivals of 71% and 71.4%, respectively.[50]

In a similar retrospective review by Remmelts et al., primary radiation therapy (89) was compared to TLM (159) in early-stage cancer of the larynx/CIS, for oncologic and functional outcome. The local control rates between the two groups were not statically different. The 5-year laryngeal preservation rate was noted to be superior in the TLM group (93% vs. 83%, $p < 0.05$), yet the overall voice handicap index (VHI) questionnaire scores reflecting superior voice results were experienced with radiation therapy ($p < 0.05$). Although patients with T1a lesions had similar VHI scores between the two treatment modalities, patients with T1b disease revealed a greater discrepancy favoring radiation therapy, likely reflecting the complexity of the resection encountered with AC lesions.[51]

In a retrospective analysis of 118 patients with cancer of the glottis (T1/T2) treated with TLM without adjuvant therapy, oncologic outcomes were assessed. The 5-year DFS and OS were 87.2% and 96.2%, respectively. On initial resection, 39.8% of patients were noted to have positive margins per the pathology report, yet when “2nd look” operations were performed (on 10 of the 43), residual cancer was not identified. Retreatment and adjuvant therapy were not offered to patients with positive margins because of the operating surgeon’s confidence in the initial acquired margins. The authors noted that in their series, AC, arytenoid, and subglottic extension did not have an impact on local control.[52]

The American College of Radiology (ACR) Expert Panel on Radiation Oncology–Head and Neck Cancer developed ACR Appropriateness Criteria for the management of T1 glottic cancer. Their guidelines advocate for TLM for T1a glottic carcinoma when the lesion can be completely visualized via a direct laryngoscopy approach. In patients with lesions less amenable to resection with TLM, radiation therapy is advocated with 2.25 Gy fractions.[53]

Laryngofissure and Cordectomy.

This open conservation laryngeal technique is reserved for T1 glottic cancers involving the mid true vocal cord and results in cure rates of >90% in selected patients. An endoscopy is performed before the laryngofissure is undertaken, and the cancer is mapped for the suitability of laryngofissure and cordectomy, following which a tracheostomy is performed. A horizontal incision in a major skinfold in the neck is used; this is separate from the tracheostomy incision. Superior and inferior flaps are raised and the larynx is exposed in the midline by separation of the strap muscles. A midline thyrotomy is then performed and the larynx opened. The lesion is then visualized and excised. The specimen is sent to the pathologist for examination by frozen section. The AC is reconstructed by anchoring the anterior end of the uninvolved vocal cord to the thyroid lamina. The perichondrium and the strap muscles are sutured together, and the incision is closed over suction drains. The increased use of endoscopic CO_2 resections has resulted in a significant decrease in the use of this open procedure.

Vertical Partial Laryngectomy.

This procedure is reserved for T1 and T2 cancers of the true vocal cord and success rates of more than 90% have been reported. The results of vertical partial laryngectomy (VPL) for selected T3 and T4 lesions have also provided acceptable outcomes. An endoscopy is performed before the VPL and the cancer is mapped for the suitability of the procedure, following which a tracheostomy is performed **(Fig. 15.8)**. A horizontal incision that is separate from the tracheotomy incision is made. Superior and inferior flaps are elevated. The strap muscles are retracted. The external perichondrium of the thyroid cartilage to be removed is incised; the perichondrium and musculature are elevated as a single flap, and the larynx is skeletonized. At this point, midline thyrotomy, cricothyroidotomy, and incision across the petiole are performed to provide visualization of the cancer. The cancer and the thyroid cartilage are then excised as one specimen (**Figs. 15.9 and 15.10**). The muscle/perichondrial flap are then used to create a neoglottis. The wound is closed over a suction drain.

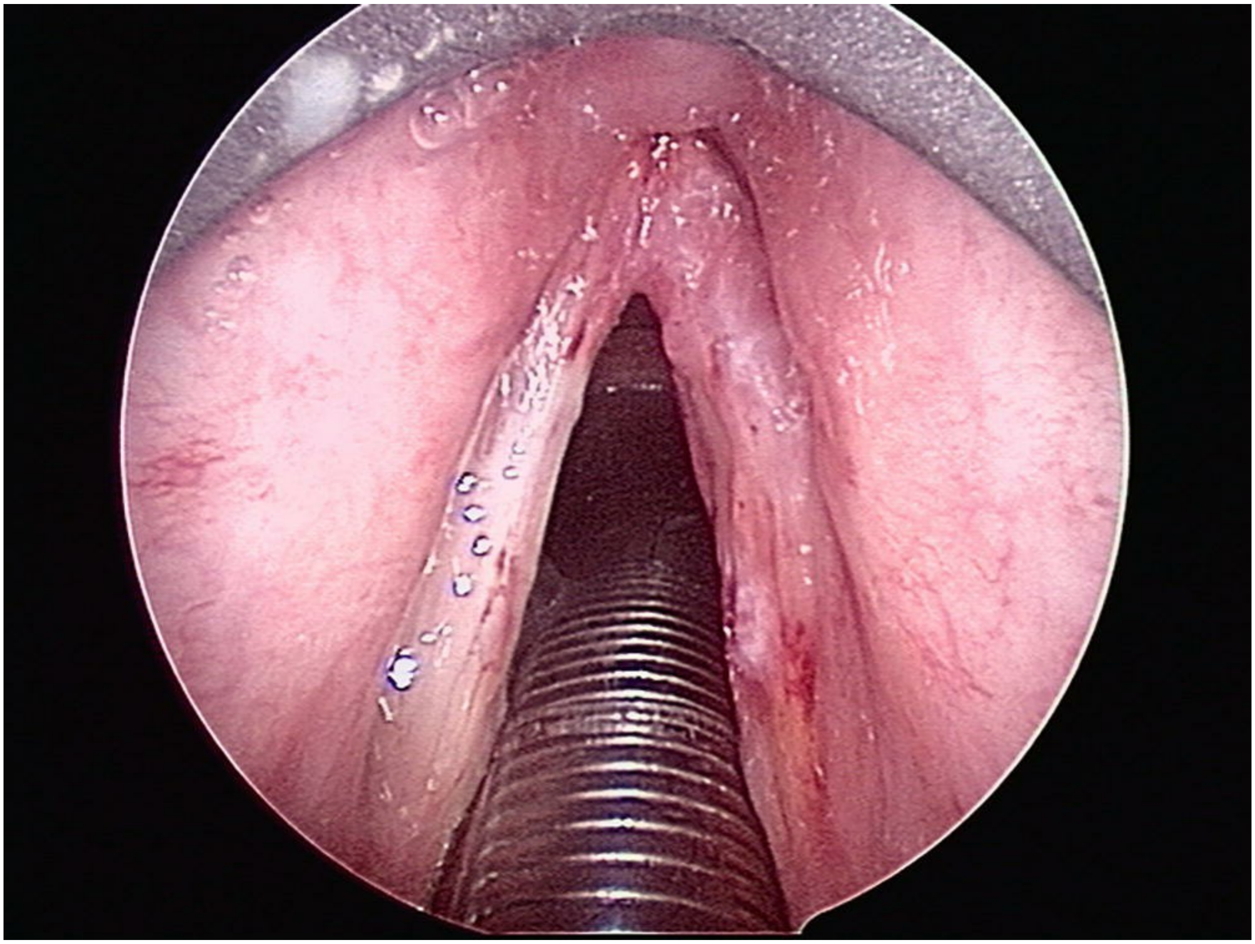

Figure 15.8. Endoscopic view of a T1b squamous carcinoma of the glottis.

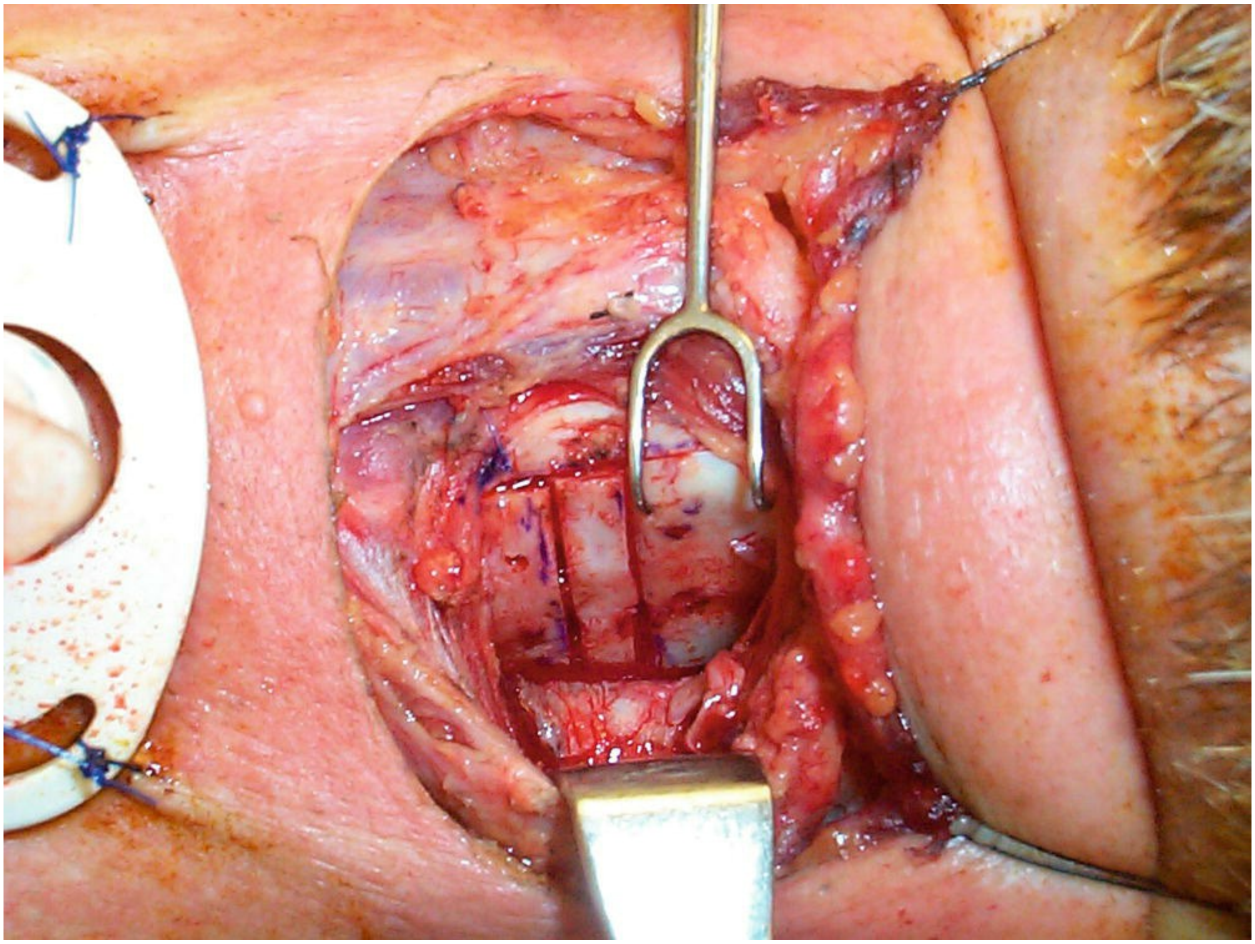

Figure 15.9. Cartilage cuts for VPL with plan for imbrication laryngoplasty.

Extended Vertical Hemilaryngectomy

1. Frontolateral vertical hemilaryngectomy—used for lesions involving the AC and the anterior contralateral cord

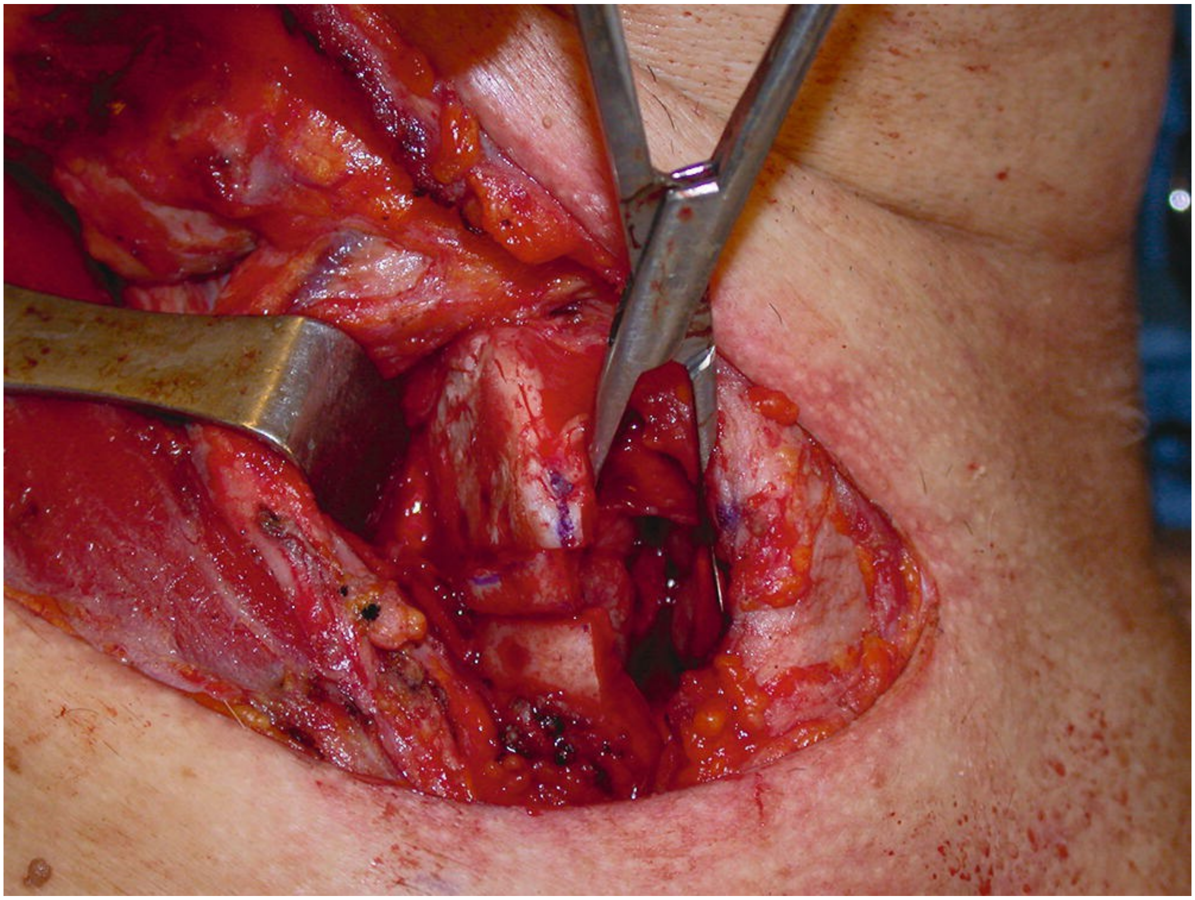

Figure 15.10. The laryngofissure performed at the time of VPL for resection of a glottic cancer provides good exposure of the larynx.

2. Posterolateral vertical hemilaryngectomy—used for lesions involving the ipsilateral arytenoid cartilage

The systematic use of frozen section control of margins cannot be overemphasized in this type of precision surgery. If frozen sections are not used and the permanent sections indicate that the margins are positive, the rate of recurrence is intolerably high.

Horizontal Glottectomy.

AC involvement has also been treated effectively with open surgical techniques. Szyfter et al. reported on their experience using open horizontal glottectomy in 108 patients with T1b disease. Negative margins were obtained in 100% of specimens with this open technique. Resection included removal of the true and false vocal cords, the lower portion of the thyroid cartilage, and the entire paraglottic space whereas reconstruction involved re-approximating the cricoid and remaining thyroid cartilage. The locoregional

recurrence rate was 16.7%, which correlated with prelaryngeal regional lymph node metastasis (6.5%). Organ preservation was possible in 90.7% of patients with a 5-year reported overall survival of 97.2%. The authors considered their results with open horizontal glottectomy comparable, if not better, than those reported by TLM and primary radiation therapy for T1b lesions.[54]

Supraglottic Carcinoma

Pressman's study of the lymphatic drainage of the subunits demonstrated that the lateral structures of the aryepiglottic folds and false cords were found to have ipsilateral lymphatic drainage and that the midline epiglottis drainage pattern was bilateral. The superficial lymphatic channels in the supraglottis had bilateral drainage, and the deep lymphatic channels were side specific. The lymphatic vessels traverse the thyrohyoid membrane, alongside the superior thyroid artery and vein, and empty into the jugulodigastric (level II) and midjugular (level III) lymph nodes.

Fibroelastic membranes within the laryngeal framework serve as functional barriers to prevent the spread of cancer from one subunit to another. These barriers include the thyrohyoid membrane, the hyoepiglottic ligament, the thyroepiglottic ligament, the conus elasticus, and the quadrangular membrane. These membranes serve to divide the larynx into two three-dimensional compartments—the preepiglottic space and the paraglottic space. Cancer initially invading the preepiglottic space can directly extend into the paraglottic space (**Figs. 15.11 and 15.12**); in this situation, the use of supraglottic laryngectomy is precluded. Involvement of these spaces has a direct effect on the selection of patients for conservative surgical management of supraglottic cancer.

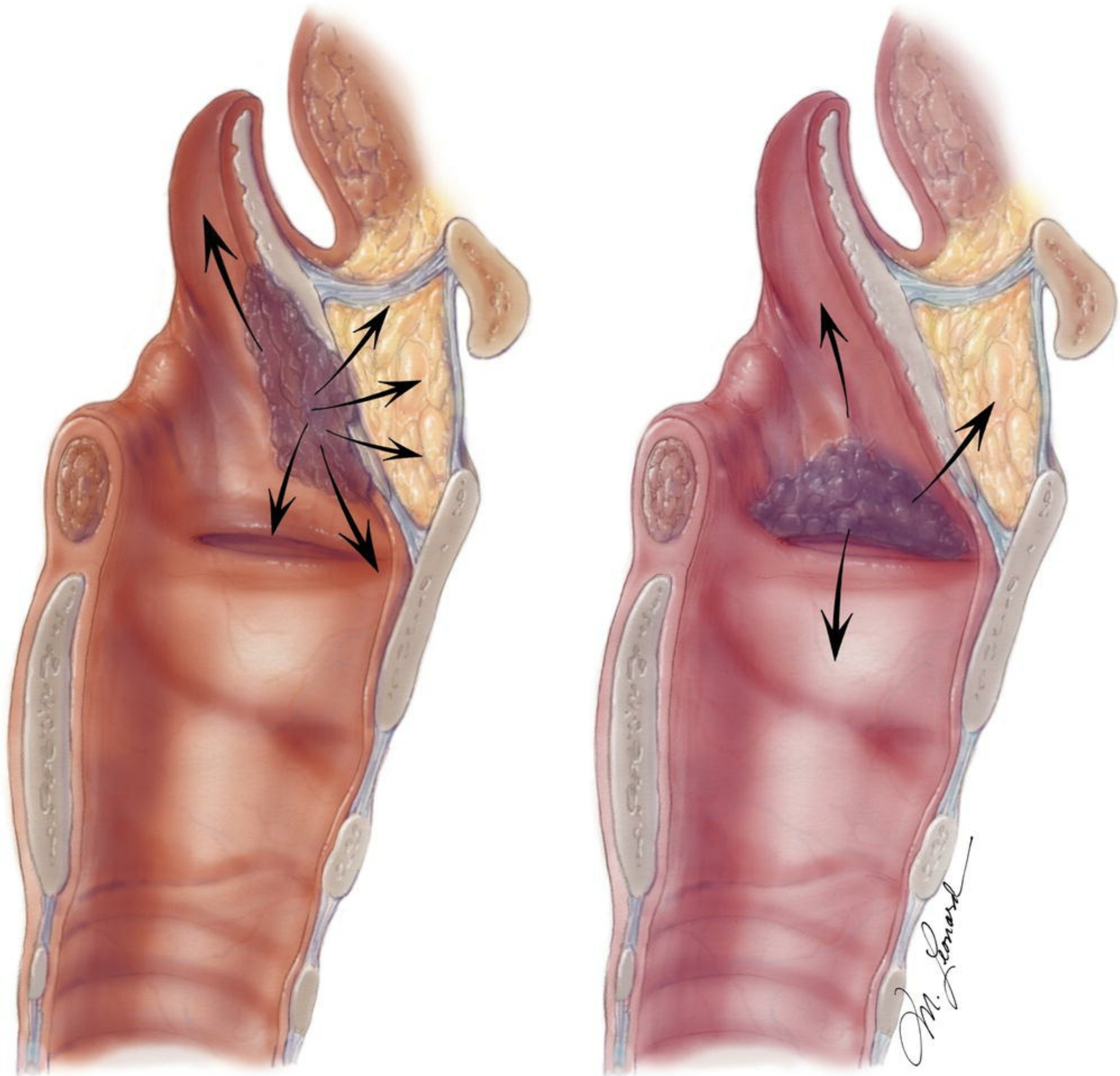

Figure 15.11. Invasion of the preepiglottic space from cancers of the laryngeal surface of the epiglottis and laryngeal ventricle.

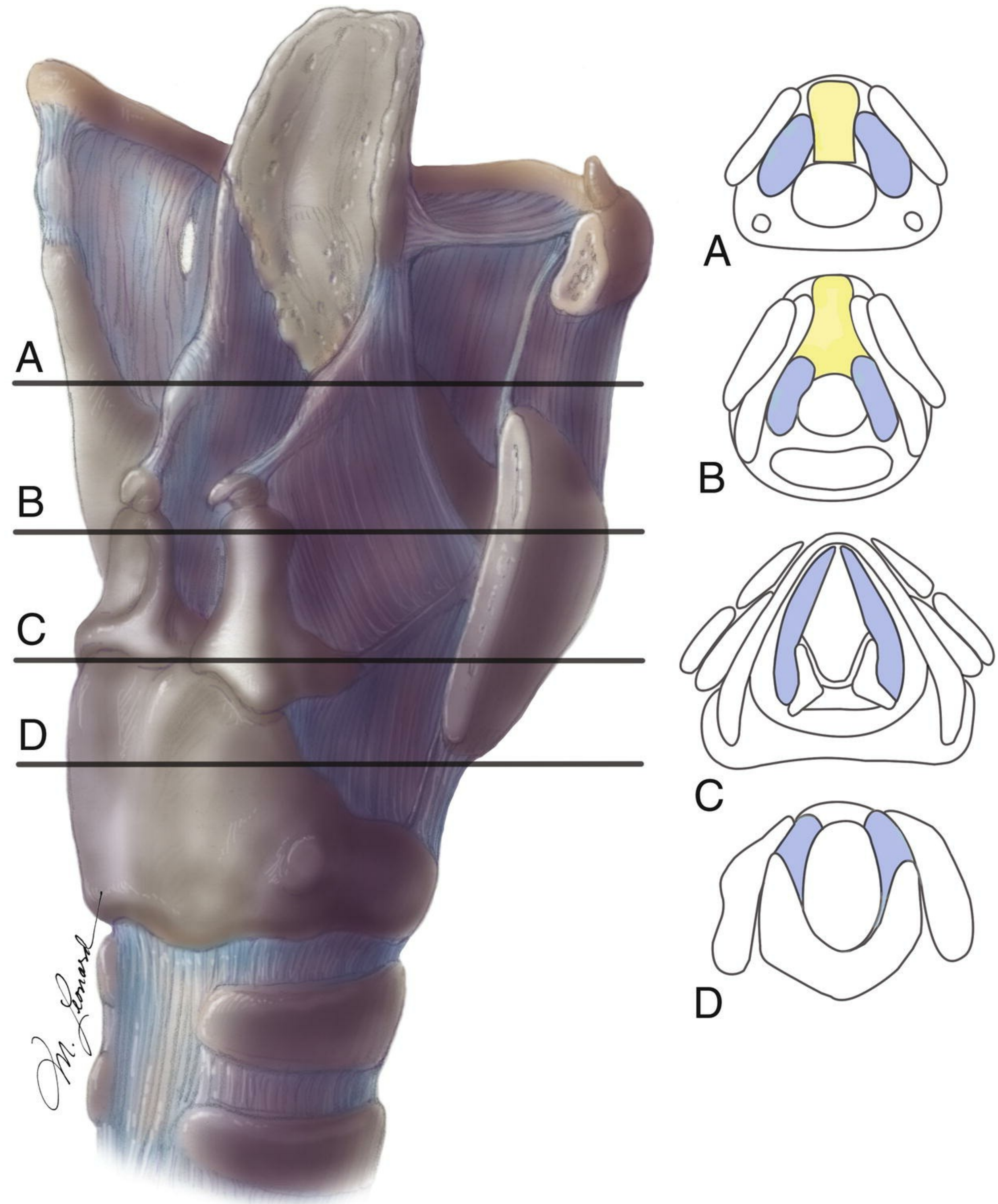

Figure 15.12. Spaces of the larynx at various axial levels. Preepiglottic space–*yellow*, paraglottic space–*blue*.

Endoscopic Resection

The concept of endoscopic management of supraglottic cancer began in 1939 when Jackson described the use of a laryngoscope and punch biopsy forceps to resect cancer of the suprahyoid epiglottis.[55] Endoscopic management fell into disrepute owing to the poor results and morbidity associated with it. The advent of the operating microscope, suspension microlaryngology, and the carbon dioxide (CO_2) laser led to the renewed popularity of endoscopic management of laryngeal cancers, both in Europe and the United States.

The potential advantages of endoscopic management over open surgery include the elimination of the need for tracheostomy, shorter operating times, and earlier rehabilitation of swallowing function. Disadvantages include the need for specialized equipment, prolonged healing time in that the defect is allowed to heal by second intention, and the potential for limited exposure that often leads to inadequate removal of the cancer. The CO_2 laser combined with an operating microscope is the most frequently used instrumentation. The quality of the voice following laser surgery for supraglottic cancer should be unchanged. Studies from Europe have shown that the results of endoscopic laser surgery are comparable to those of radiation therapy, with the latter type of treatment being more convenient for patients and less expensive overall.

The use of endoscopic laser resection is dependent on the size, location, and extent of the cancer. T1 and T2 cancers located on the suprahyoid epiglottis, aryepiglottic fold, and vestibular fold with minimal preepiglottic and no paraglottic involvement can be treated successfully with endoscopic resection. Cancers arising on the infrahyoid epiglottis and false cord can be technically challenging to resect with endoscopic resection. The most important factor in endoscopic laser surgery is adequate exposure of the cancer. The use of the Weerda bivalved laryngopharyngoscope allows optimal exposure. The superior blade is placed into the vallecula, and the inferior blade pushes the endotracheal tube against the posterior pharyngeal wall. The laryngoscope is repositioned as necessary to maintain optimal exposure throughout the procedure.

The CO_2 laser is the laser of choice for endolaryngeal surgery. Advantages of the CO_2 laser include its superficial effect, which helps to minimize damage to surrounding normal tissue, and its ability to be used as a cutting tool in the focused mode and as a coagulation tool in the defocused

mode.

Small cancers on the suprahyoid epiglottis or the aryepiglottic fold may be resected with the laser en bloc, but the majority of supraglottic cancers are excised in a piecemeal fashion. The epiglottis is split in the midline (sagittal plane) with resection of the suprahyoid division first, followed by the infrahyoid component. The preepiglottic adipose tissue is then encountered and removed until the thyrohyoid membrane is identified. Resection is then continued inferiorly to include the aryepiglottic folds and false cords as necessary. Frozen sections are taken from the specimens, and additional resection is performed until negative margins are achieved. The defect is allowed to heal by second intention (**Fig. 15.13**).

Figure 15.13. Endoscopic appearance after TLM resection of an epiglottic carcinoma with appropriate wound healing.

A retrospective study examining the feasibility of TLM in cases of T3 cancer of the larynx was reported by Canis et al. in a series of 226 patients (glottic 122, supraglottic 104). Adjuvant radiation was required in 18% of patients and 63% underwent delayed neck dissection. Endoscopic CO_2 laser resection to a margin of 2 to 3 mm was pursued with primary cancers of the glottis and expanded to 5 to 10 mm for supraglottic tumors. Postoperative bleeding

occurred after 1% of glottic resections and 12% following supraglottic procedures. The 5-year laryngeal preservation rate was 87%. The 5-year local control and overall survival rates were 71.4% and 64.4%, respectively. The authors emphasized the favorable oncologic results with limited treatment-related morbidity and capacity for organ preservation offered by TLM when compared to chemoradiation and open surgical techniques.[56]

Potential complications of endoscopic excision include intraoperative or postoperative hemorrhage and infection of the exposed laryngeal cartilage.[55] Radiation may be started ~2 to 4 weeks following resection of the primary. The patient is readmitted for neck dissections. At that time, further resection can be carried out if permanent sections reveal positive margins.

Supraglottic Laryngectomy

Supraglottic laryngectomy is indicated in patients in whom the cancer arises from the epiglottis, aryepiglottic folds, and false vocal cords. This procedure minimizes morbidity and maintains the three primary functions of the larynx—airway protection, respiration, and phonation. Supraglottic laryngectomy (as a two-stage procedure) was introduced by Alonzo in 1947 as an alternative for supraglottic tumors to the traditional total laryngectomy and radical neck dissection. Modifications made by Ogura in 1958 and later by Som in 1959 converted supraglottic laryngectomy to a one-stage procedure.[55]

The most important factor influencing the success of supraglottic laryngectomy is appropriate patient selection based on both the patient and tumor factors. Every patient undergoing supraglottic laryngectomy will experience temporary aspiration postoperatively, thus making the patient’s cardiopulmonary reserve an important factor in patient selection. Patients must have a reasonably good cough mechanism or they will not be able to swallow properly and will therefore aspirate and potentially develop recurrent aspiration pneumonia and become malnourished.

The cancer factors are equally important in the selection process; established contraindications are based on anatomic considerations, including involvement by cancer of the thyroid cartilage or the AC, vocal cord fixation due to involvement of the paraglottic space, and involvement of the sinus apex pyriform or postcricoid mucosa. Such patients are at an unacceptable risk because of the potential for recurrent cancer, as well as the potential for

postoperative dysphagia and aspiration. In patients with involvement of the base of the tongue, primary closure can be difficult, resulting in increased dysphagia and aspiration.

Supracricoid Partial Laryngectomy

SCPL remains a surgical treatment alternative for selected patients for the primary treatment and surgical salvage of glottic (with cricohyoidoepiglottopexy [CHEP]) and supraglottic carcinoma (with cricohyoidopexy [CHP]). Beyond anatomic considerations, comorbidities that would be a contraindication to the procedure include compromised pulmonary function (e.g., COPD) and disorders predisposing to poor wound healing such as insulin-dependent diabetes, selected immunologic disorders, and severe peripheral vascular disease.

Placement of a gastrostomy tube prior to surgery should be considered anticipating postoperative dysphagia and aspiration that requires a prolonged period of rehabilitation with the assistance of a speech–language pathologist. Preoperative placement of a gastrostomy tube is strongly advised for patients over 75 years of age, individuals requiring resection of one arytenoid at the time of operation, patients who have been previously radiated, and patients with CN XII, superior or recurrent laryngeal nerve dysfunction or need for sacrifice of these nerves. A temporary tracheostomy is placed at the time of surgery with the goal of early decannulation to facilitate laryngeal elevation and minimize inhibiting a patient's cough reflex as they adapt to the postsurgical changes as they regain their ability to swallow.[57]

In SPL-CHP, the entire supraglottis, the false and true vocal cords, and the thyroid cartilage, including the paraglottis and preepiglottic spaces, are removed. The procedure can be extended to resect one involved arytenoid cartilage. The cricoid cartilage, hyoid bone, and at least one arytenoid are saved. Phonatory and swallowing functions are maintained by the movement of the remaining arytenoid against the base of the tongue.

In SCL-CHEP, the false and true vocal cords and the thyroid cartilage, including the paraglottic, are removed. Reconstruction is performed by suturing the hyoid bone and the remnants of the epiglottis to the cricoid cartilage.

SCL can be used as a primary treatment modality or as a salvage option

after failure of organ preservation therapy (radiation therapy or radiation therapy with chemotherapy). SCL-CHP has a high rate of failure (aspiration and tracheotomy dependence) after radiation therapy with chemotherapy. SCL may be considered for supraglottic cancers that involve the glottis at the AC, invade the thyroid cartilage, are associated with impaired vocal cord mobility, and have paraglottic invasion and/or moderate preepiglottic space involvement or are transglottic (**Figs. 15.14 to 15.16**).

Figure 15.14. Incisions made through the FVC/TVC during a supracricoid

laryngectomy with CHP for a supraglottic carcinoma.

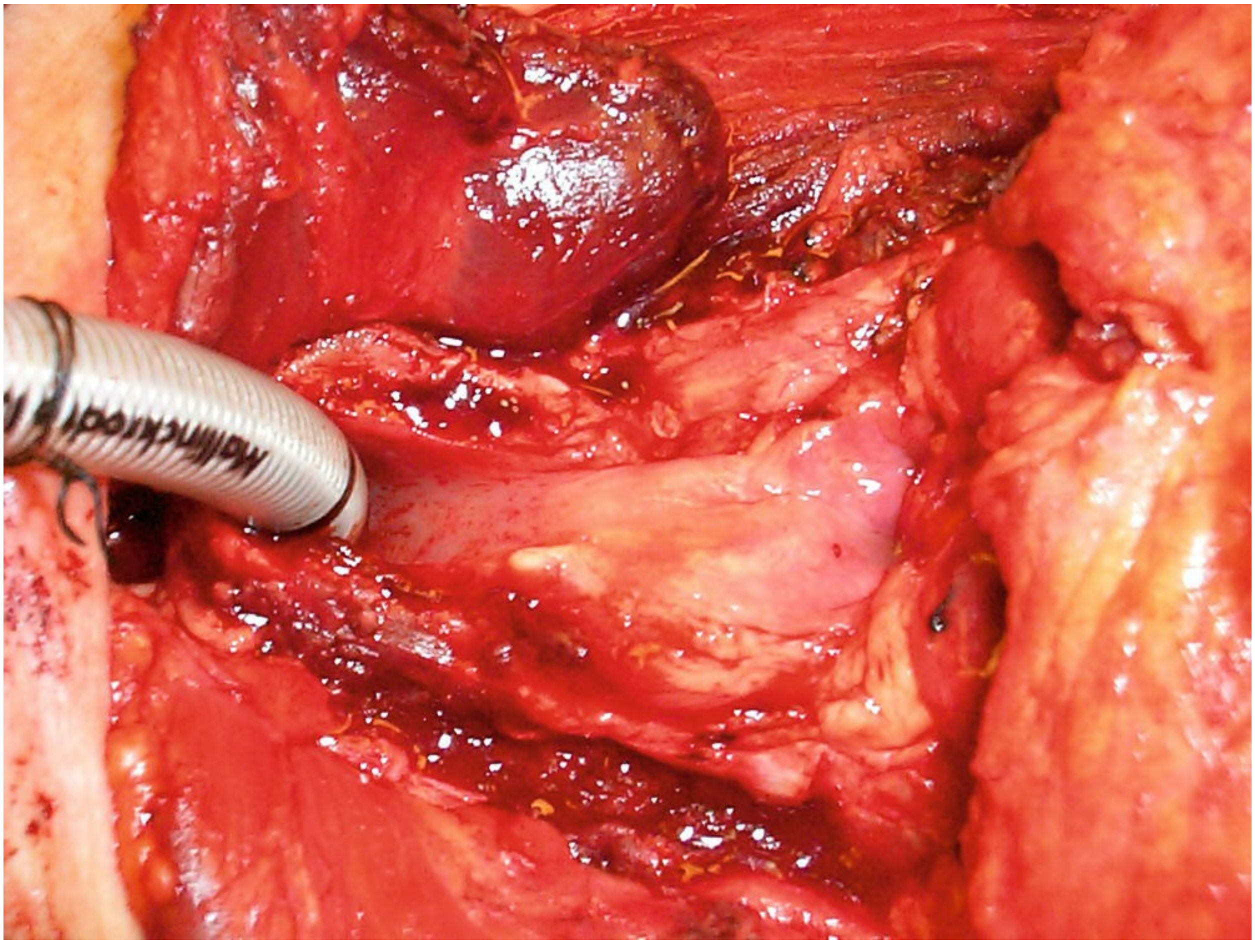

Figure 15.15. Operative picture of remaining anatomy after supracricoid resection. The left arytenoid was preserved.

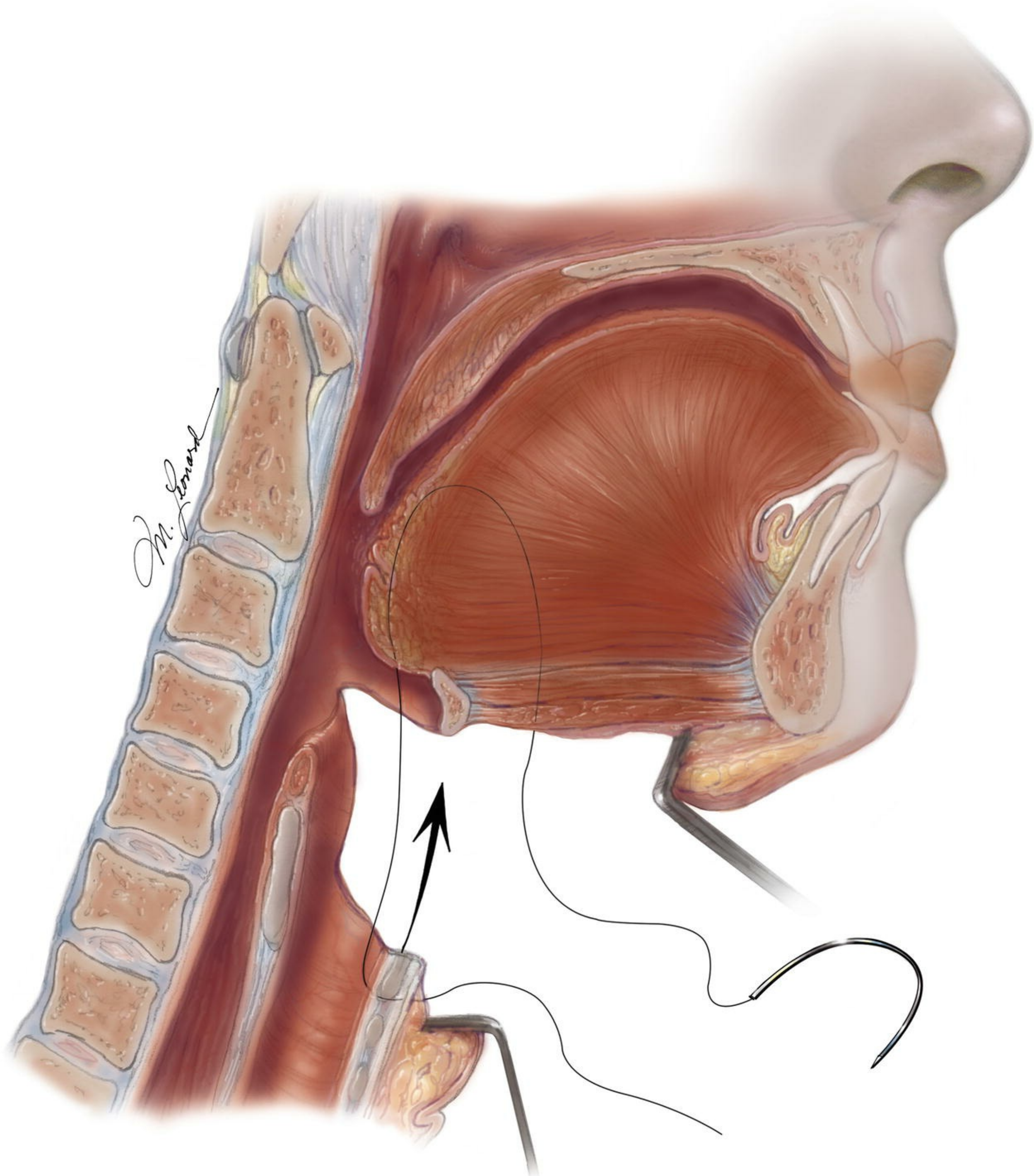

Figure 15.16. Sagittal view–suture placement, approximating cricoid to hyoid, made during reconstruction with a supracricoid laryngectomy with CHP.

Total Laryngectomy

Despite the advances made in organ preservation treatment protocols, total laryngectomy (TL) is a viable option in certain patients, including those with locally advanced cancer of the larynx with cartilage invasion, recurrent or persistent cancer after conservation treatment (surgery, radiation therapy, or chemoradiotherapy), and advanced malignant tumors of certain histologic types such as spindle cell carcinoma, adenocarcinoma, chondrosarcoma, and others that respond poorly to radiation therapy and/or chemotherapy. It is also appropriate for those with benign processes such as chronic severe aspiration or radionecrosis of the larynx refractory to more conservative management (**Figs. 15.17 to 15.20**).

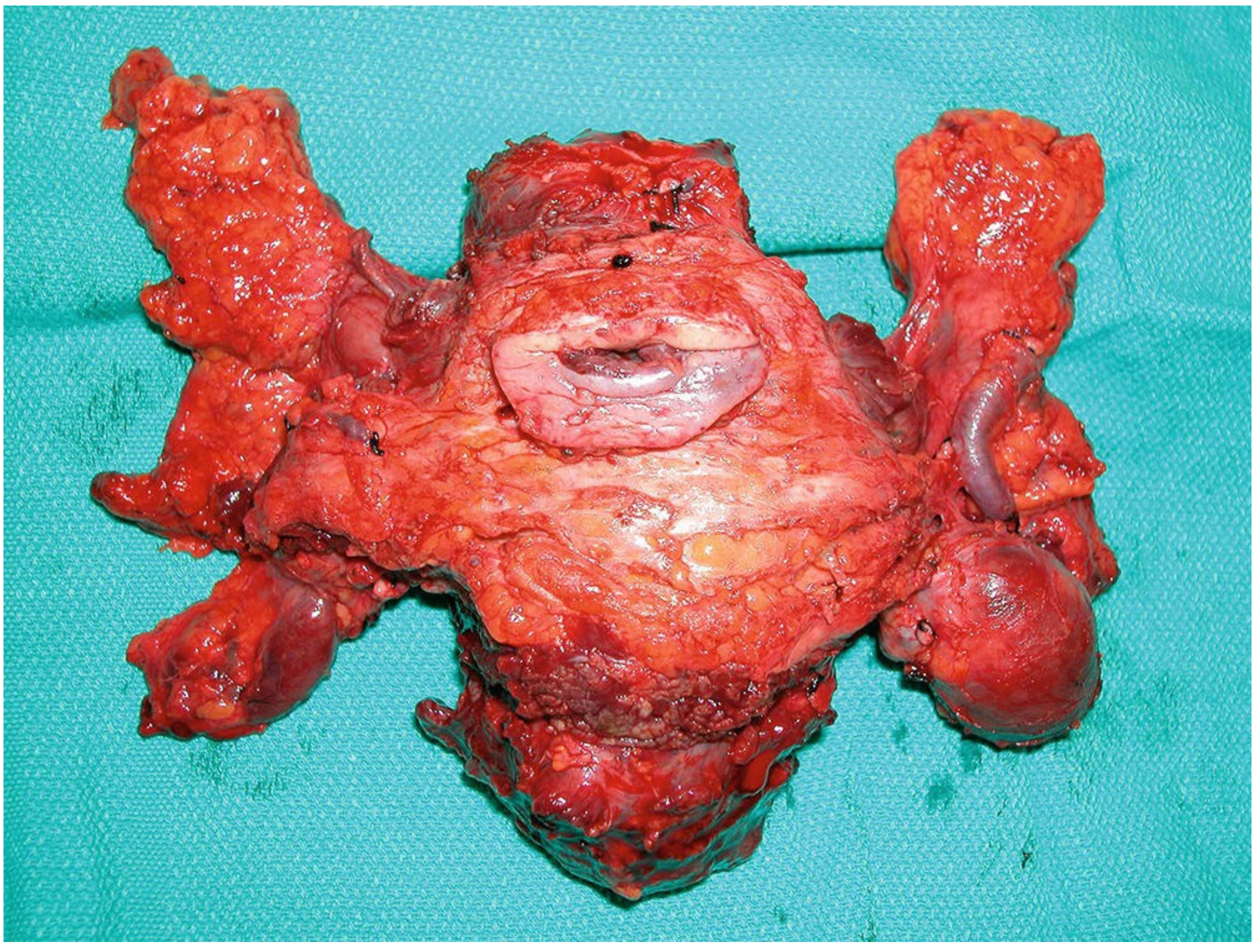

Figure 15.17. Total laryngectomy specimen (anterior view) with attached bilateral selective neck dissections. Skin around the prior tracheostomy site is incorporated into the resection specimen.

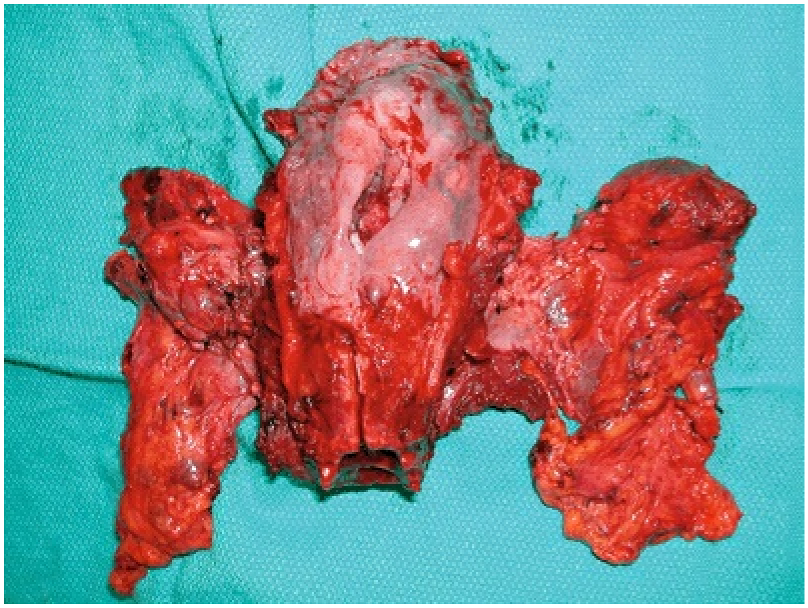

Figure 15.18. Total laryngectomy specimen (posterior view) showing the mucosal margins from the pharyngeal component of resection for a large, transglottic, obstructing cancer.

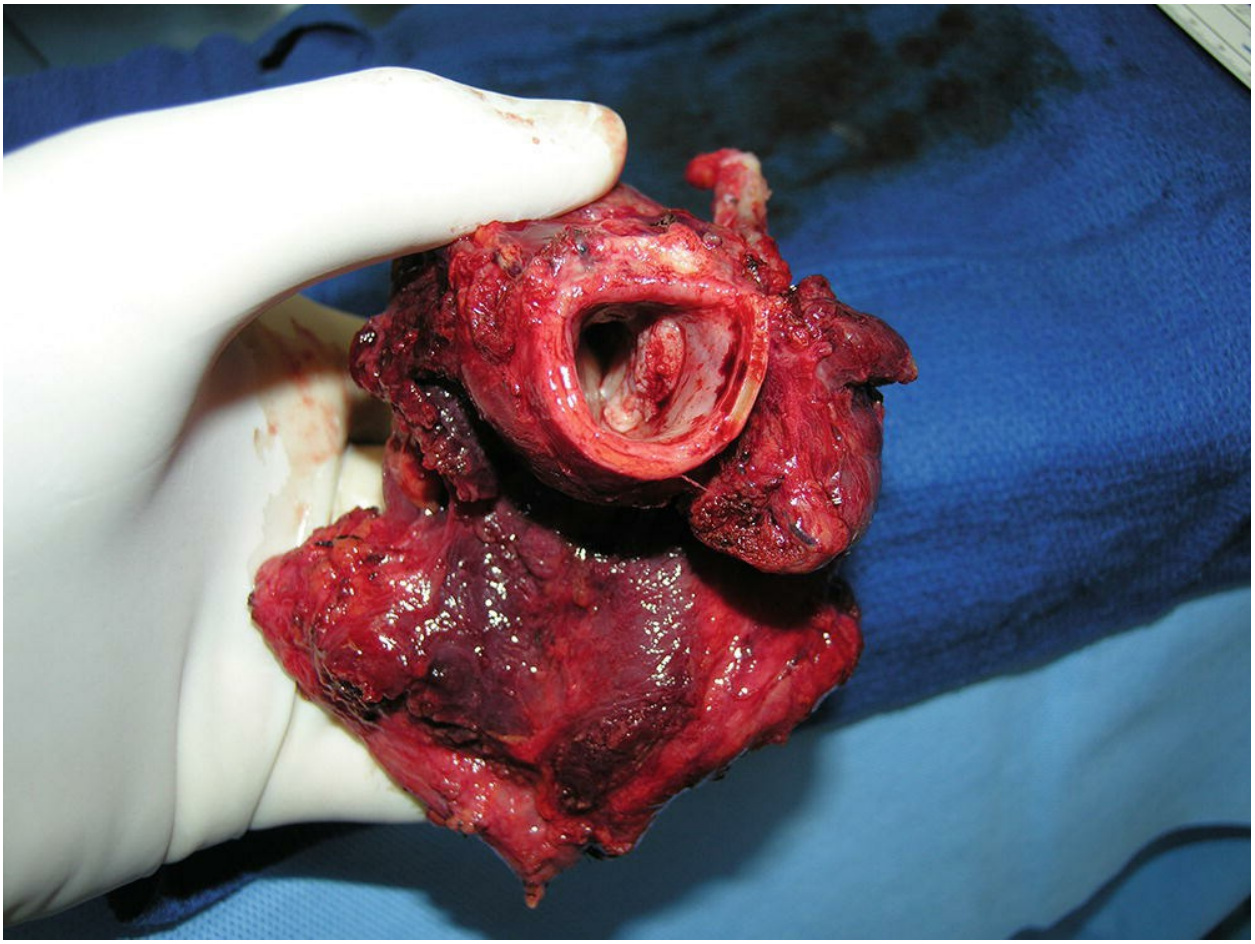

Figure 15.19. Total laryngectomy specimen demonstrating subglottic extent of tumor looking into the trachea.

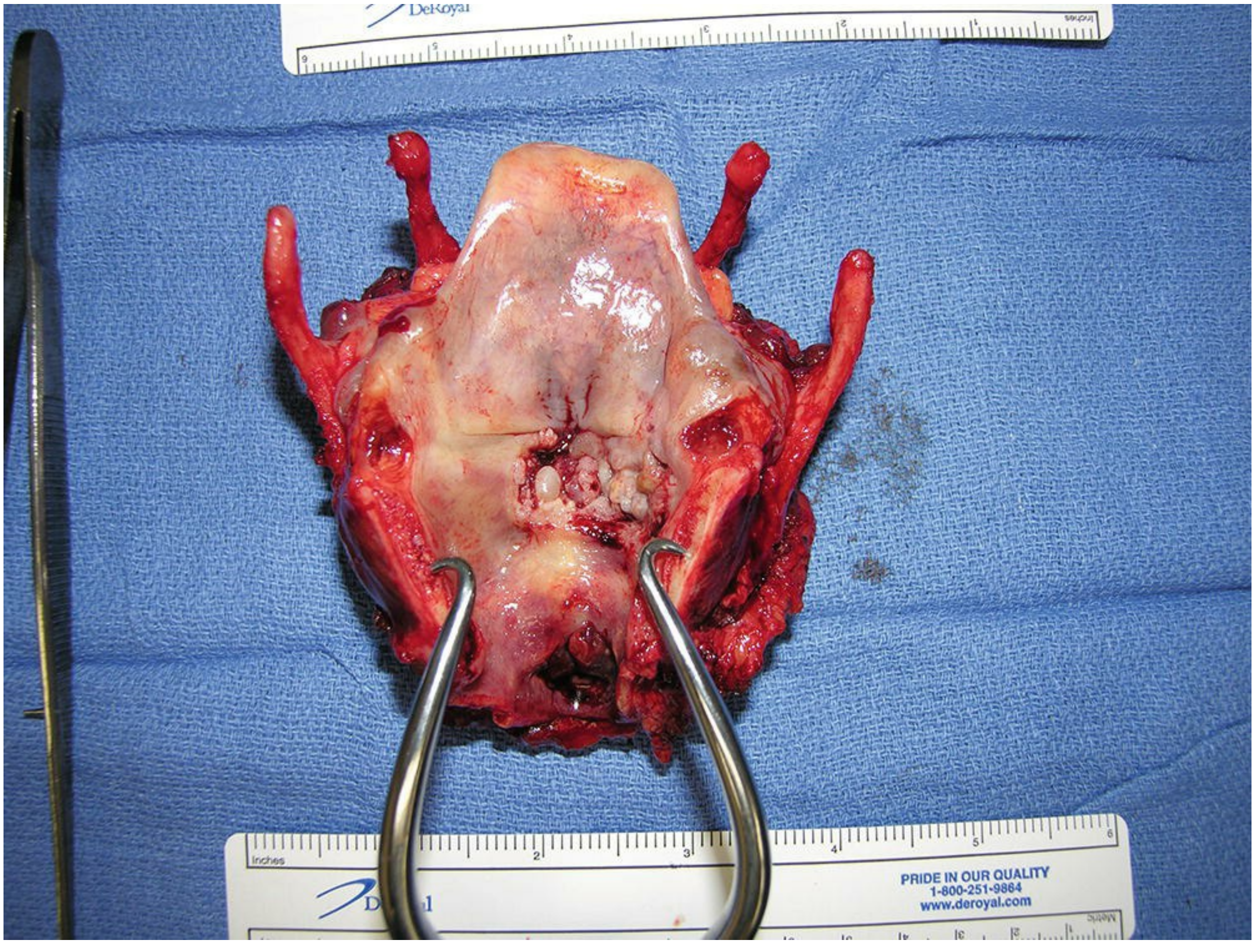

Figure 15.20. Total laryngectomy specimen with posterior cricoid cartilage bisected demonstrating extent of spread of a transglottic cancer that had preepiglottic and paraglottic space spread.

Criteria for patient selection for TL include the ability of the patient to undergo general anesthesia and to care for the stoma, as well as the psychological capability for adjusting to a laryngectomy.

Robotic Laryngeal Surgery.

Transoral robotic surgery (TORS) has been applied to resection of cancer of the larynx. Lallemant et al. reported on a series of 23 patients (13 glottic, 10 supraglottic) with predominantly early-stage cancer (T1N0-16, T2N0-4, T2N+-3) treated with primary TORS. The local recurrence rate was 8.7% (2/23) and was associated with cancer of the AC in both cases. The median operative time was 1 hour and patients were hospitalized a median of 7.5 days. There were no intraoperative complications. There were two reported

postoperative complications including one case with cervical emphysema with pneumothorax and laryngeal bleeding requiring a return to the operating room and a second case with supraglottic bleeding on postoperative day 2 requiring a return to the operating room for control. As a result of their experience, the authors recommend pre-emptive identification and clipping or coagulation of the superior laryngeal artery when supraglottic resections are performed. The oncologic results of TORS resection for this population were comparable to endoscopic CO_2 laser resection.[58]

Park et al. reported on 16 previously untreated patients who underwent primary TORS supraglottic partial laryngectomy. The majority of cancers were epiglottic (62%) with the remainder located on the aryepiglottic fold (25%) and false vocal fold (13%). The cancers were predominantly early staged (T1–T7, T2–T5, T3–T4) and 56% of patients were N0. Neck dissections (eight unilateral, six bilateral) were performed concurrent with the TORS. A temporary tracheostomy was placed in all patients. Negative margins at the time of resection were obtained in 88% of patients. One-half of patients required adjuvant therapy with 31% also requiring chemoradiation. Patients resumed the capacity to swallow after an average of 8.3 days and the average hospital stay was 13.5 days. There were no significant perioperative or postoperative complications reported. The Kaplan-Meier disease-free survival for the group at 2 years was 91%.[59]

TORS is not limited to partial laryngeal surgery; a series of patients who underwent TORS total laryngectomy was reported by Smith et al. The technique was used in a group of 7 patients with recurrent cancer (5/7) or posttreatment laryngeal dysfunction (2/7). At the beginning of the TORS approach, a transcutaneous incision is made to allow for tracheal transection and creation of the stoma. The surgical resection of the larynx and associated pharyngeal tissues is accomplished with the transoral technique in addition to the pharyngeal mucosal closure after removal of the specimen. The surgical approach requires adequate exposure to the vallecula and does require resection of the hyoid as part of the procedure. TORS total laryngectomy required conversion to an open approach in 29% of patients due to inadequate exposure with the robotic approach. Postoperative fistula occurred in 29% of patients. The authors cite that patients with a narrow mandibular arch, anterior displacement of their laryngeal anatomy, and intact dentition would not be candidates for this approach. They also state the exact indications and

limitations of the technique continue to evolve, yet they believe that the technique has a role in salvage surgery for the larynx.[60]

Complications of Laryngectomy

Early Complications

Early complications of laryngectomy include infection, stomal crusting, and pharyngocutaneous fistula. Perioperative antibiotics have significantly decreased the incidence of infection. Crusts around the stoma are removed at least once a day to prevent airway obstruction.

Fistula formation occurs in 15% to 40% of cases, depending on whether regional flaps are used for pharyngeal closure and whether the tissues have been previously radiated. The fistula itself is conservatively managed with drainage, irrigation, and packing; most heal spontaneously. Fistulas in patients who had undergone previous irradiation were larger than in patients who had not had prior treatment.[61]

Free-tissue transfer reconstruction of the hypopharynx is the preferred method of reconstruction following combined chemotherapy and radiation therapy protocols (**Figs. 15.21 to 15.23**). Surgical complications such as pharyngocutaneous fistulas are significantly reduced, and hospital stays are minimized with the use of microvascular flap reconstruction.[62]

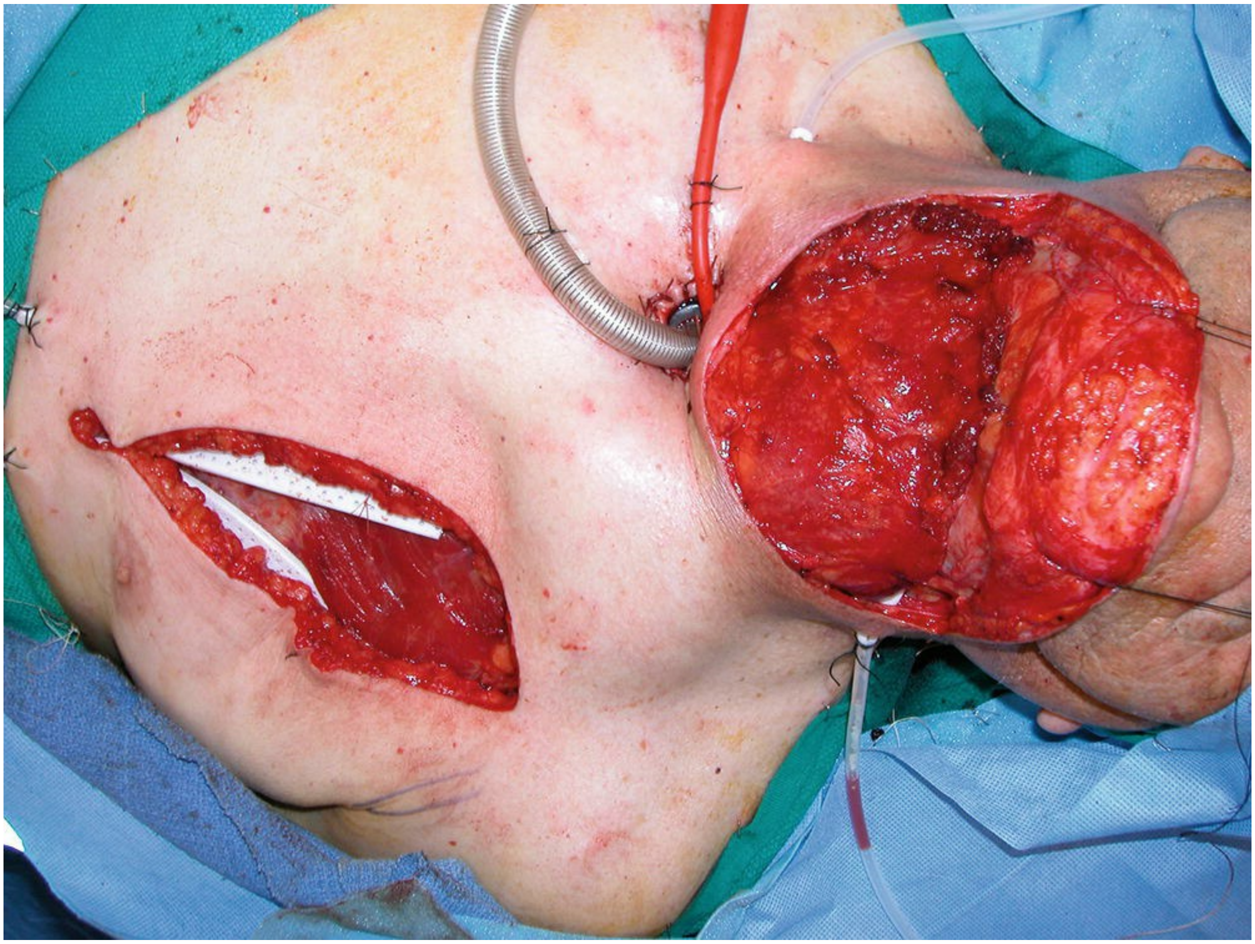

Figure 15.21. Pectoralis major (muscle-only) overlay flap used at the time of salvage laryngectomy after recurrence despite prior treatment with chemoradiation. Primary pharyngeal mucosal closure was performed without flap augmentation.

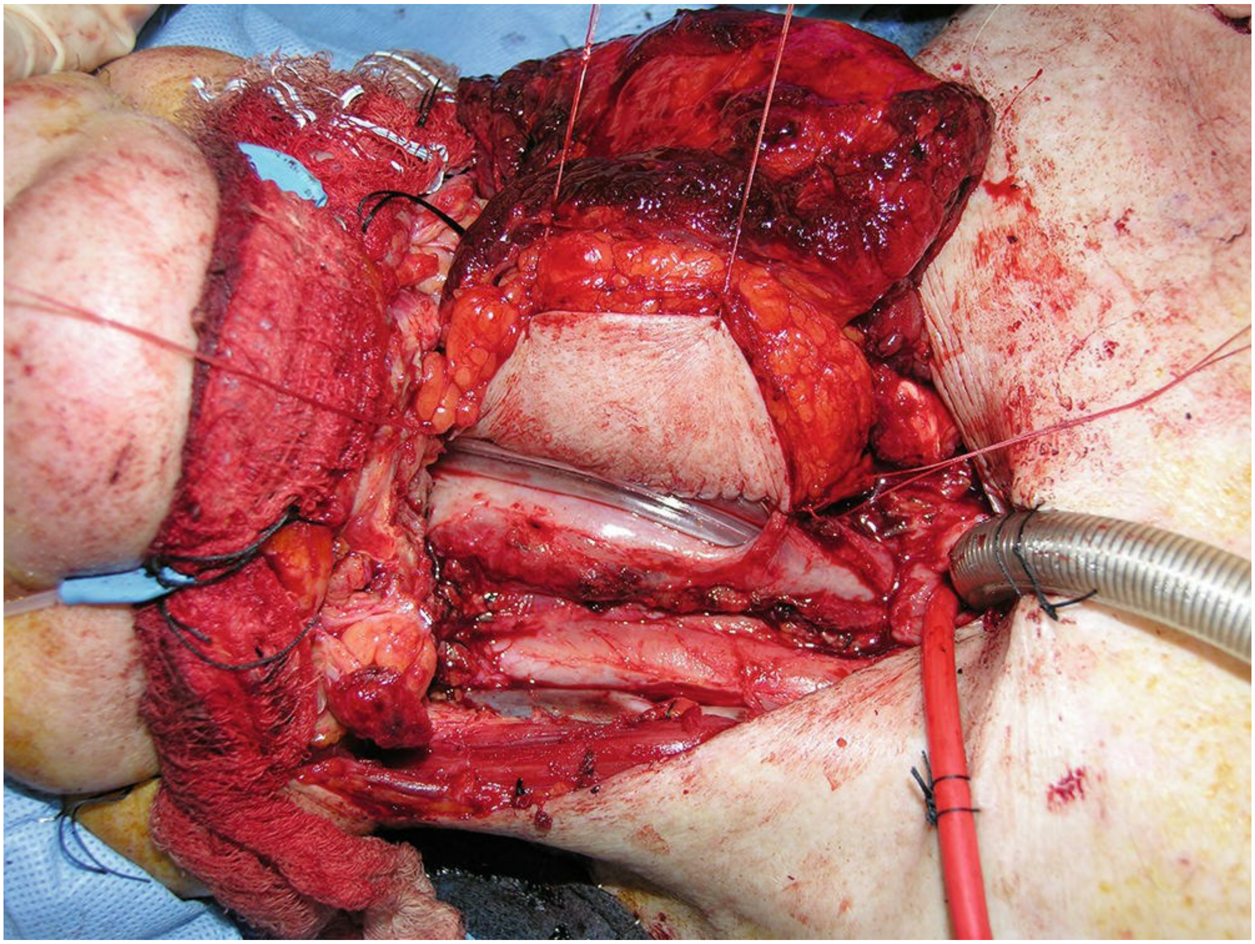

Figure 15.22. Pectoralis major flap ("patch") reconstruction of a partial pharyngeal defect in a patient requiring primary laryngectomy and partial pharyngectomy.

Figure 15.23. Tubed radial forearm free flap reconstruction of a pharyngeal defect after total laryngopharyngectomy (prior to arterial/venous anastomosis).

The most feared complication of a salivary fistula is carotid artery blowout from exposure of the artery and infection in the wound. The high morbidity and mortality associated with urgent carotid ligation have led many to employ routine coverage of the carotid artery in all cases in which laryngectomy is performed after radiation therapy is provided. The sternocleidomastoid muscle often provides adequate coverage. If the muscle has been removed during a concomitant radical neck dissection, dermal grafts and regional flaps have been described either to provide coverage for the artery or to direct the flow of saliva away from the artery.

Late Complication

Late complications following laryngectomy include stenosis of the stoma and

a stricture of the pharyngeal remnant with dysphagia. Stenosis of the tracheostoma is a frequent complication following total laryngectomy that results in reduced airflow. Many authors have attempted to identify factors associated with stomal stenosis; a number of procedures have been recommended for the surgical correction of such stenosis.[63,64]

Dysphagia that develops gradually during the postoperative period is often a sign of pharyngeal stenosis; however, recurrent cancer must first be ruled out. Barium esophagogram is helpful in revealing the site of narrowing, but endoscopy with biopsy under general anesthesia is required to determine if the stricture is recurrent cancer or benign scarring. Benign strictures can usually be managed with serial dilations, but occasionally, patients require excision of the stenotic pharynx with pharyngoesophageal reconstruction and regional or free-tissue transfer.

The number of deaths in patients with laryngeal cancer is generally higher in those with supraglottic primary cancers, more so than glottic, and increasingly related to intercurrent diagnoses, long-term complications of treatment (aspiration pneumonia), and the development of metachronous primary cancers.[65] The distant metastatic rate for patients with cancers of the larynx is generally lower than other sites in the head and neck and is ~8%.

Voice Rehabilitation After Total Laryngectomy

A major challenge faced by the head and neck surgeon and the speech pathologist in treating a patient who has had a total laryngectomy is the restoration of speech. The first artificial larynx was devised by Gussenbauer in 1874. Voice restoration using the fistula technique was reintroduced by Asai in 1965. In 1979, Singer and Blom introduced the tracheoesophageal puncture (TEP) and silicone prosthesis for generating tracheoesophageal voice.

The patient who is undergoing a total laryngectomy is offered three options: the artificial larynx or electrolarynx, esophageal voice, and tracheoesophageal voice.

Electrolarynx

The artificial larynx is available as an external device that is placed against the neck or as an oral type. Both types are electrically driven and produce a mechanical sound. This sound is articulated by the tongue, lips, and teeth as understandable speech. Advantages of the electrolarynx include the short learning time required for its use, its ability to be used during the immediate postoperative period, and its relative availability and low cost. Disadvantages include its mechanical sound and dependence on batteries, as well as the need for maintenance of the intraoral tubes.

Esophageal Voice

A speech pathologist or another laryngectomy patient usually teaches the patient insufflation behavior in acquiring esophageal speech. This entails trapping air in the mouth or pharynx and propelling it into the esophagus. This produces a belch-like sound that can be articulated by the tongue, lips, and teeth. The patient learns how to rapidly insufflate and eject air through the esophagus to produce understandable speech.

Tracheoesophageal Voice

Tracheoesophageal speech is considered by many to be the preferred modality for rehabilitation of a patient following laryngectomy. It is based on the concept of shunting of tracheal air to the pharynx through a controlled fistulous tract during exhalation to produce sound through vibration of the mucosa of the upper esophageal segment. Speech is produced by articulation of this sound at the level of the oral cavity.[66]

Technique of Tracheoesophageal Puncture

TEP can be performed at the time of laryngectomy (primary TEP) or later as an independent procedure (secondary TEP). The timing of TEP is an area of debate and is usually based upon the surgeon’s preference. Primary TEP offers the advantages of avoiding a secondary procedure and providing early voice rehabilitation; the transesophageal fistula can be used temporarily as a feeding esophagostome. Primary TEP is performed after the stoma has been constructed and before the pharynx has been closed.

The most common problem following TEP is failure of voice restoration. Studies have shown that failure rates range from 3% to 15%. Some of the common causes of failure of voice restoration following TEP include inadequate patient motivation and learning capabilities. In addition, patients with poor vision, arthritis, or neurologic disabilities have been found to be poor candidates for the procedure. In many instances, patients may be fitted with a hands-free, self-retaining unit that precludes the need for digital manipulation of the stoma. These conditions should be considered during the preoperative evaluation of the patient by a speech pathologist.

Another cause of failure is pharyngoesophageal spasm, which appears to be caused by reflex contraction of cricopharyngeal constrictor muscles when the mid-esophagus is distended with air. It is believed to be a cause of TEP speech failure in 10% to 12% of patients. Therapeutic options for pharyngoesophageal spasm include cricopharyngeal and constrictor myotomies, pharyngeal neurectomies, and injection of the pharyngeal muscles with botulinum toxin.

Other complications resulting from TEP include bleeding from around the tract (usually granulation tissue), air in the stomach, salivary leakage around or through the prosthesis, and aphonia during radiation therapy. More serious and potentially life-endangering, although fortunately rare, complications include mediastinitis, cervical cellulitis, and aspiration of the prosthesis.[67]

Radiation Therapy for Cancer of the Larynx

Radiation therapy has a long history as a key component of treatment for cancer of the larynx[68] and may be used as a single modality in definitive therapy or in combination with surgery and/or chemotherapy, depending on patient and disease factors.

Indications and Techniques

Early Cancer of the Glottis (Stage I and II Disease)

Radiation therapy alone is a standard, effective treatment option for the majority of early squamous carcinomas of the glottis, and supporting data for this approach are largely based on institutional reports. Investigators from the University of Florida reported 5- and 10-year local control rates of 94% and 93% for T1a, 93% and 91% for T1b, 80% and 80% for T2a, and 70% and 67% for T2b following radiation therapy, respectively.[69] These results compare favorably to other large contemporary institutional series (**Table 15.3**). Overall, the rates of local control following radiation therapy compare favorably with modern surgical outcomes[80] (3), and severe complication rates following radiation therapy are quite low (<2%)[69] (2). As for early invasive carcinomas, radiation therapy can be an effective treatment for extensive or recurrent CIS of the glottis, with expected control rates exceeding 90%.[81]

Table 15.3 Local Control Rates at 5 Years for Early Glottic Carcinomas Following Radiation Therapy, According to T Category

First Author, Year	Follow-up	*n*	T1a	T1b	T2a	T2b
Chera et al., 2009[69]	Median 12 y	585	94%	93%	80%	70%
Nomiya et al., 2008[70]	Median 7.4 y	163	92%	85%		
Groome et al., 2006[71]	Median 5.9 y	704	82%	82%	63%	63%
Cellai et al., 2005[72]	Mean 9.3 y	831	84%	81%		
Frata et al., 2005[73]	Mean 7.5 y	256			73%	73%
Cho et al., 2004[74]	Median 14.4 y	246	83%	83%	62%	62%
Gowda et al., 2003[75]	Median 5.8 y	200	93%	89%		
Garden et al., 2003[76]	Median 6.8 y	230			74%	70%
Warde et al., 1998[77]	Median 6.8 y	735	91%	82%	69%	69%
Le et al., 1997[78]	Median 9.7 y	398	85%	85%	70%	70%
Burke et al., 1997[79]	Median 5.25 y	102	92%	80%	94%	23%

Adapted from Chera BS, Amdur RJ, Morris CG, et al. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;78(2):461–466, with permission.

Nearly all T1–T2N0 tumors are suitable for radiation therapy–based treatment, but a number of patient (e.g., anemia and smoking), cancer (e.g., anterior or posterior commissure involvement, bulky cancers, impaired vocal cord mobility, and subglottic extension), and treatment factors (e.g., lower daily dose, prolonged overall treatment time, smaller field size, and use of higher-energy photons) have been reported to negatively influence local

control in various series.[72,76–78,82] Radiation oncologists must take great care to identify potentially modifiable risk factors and eliminate any potential technical causes of treatment failure, such as geographic miss, low radiation dose given volume of cancer, and improper technique.[83] It is notable that patients irradiated for early glottic cancers are far more likely to die of a second primary upper aerodigestive tract cancer than their index larynx cancer, which has implications for long-term follow-up and survivorship care.[72]

Generally, compared to T1 cancers, reported absolute local control rates fall ~10% to 25% when vocal cord mobility is impaired (i.e., T2b disease). A number of radiation therapy intensification approaches have been pursued to improve results, most commonly through the use of altered fractionation radiation schedules (acceleration and/or hyperfractionation). For example, the Radiation Therapy Oncology Group (RTOG) trial 95-12 randomized patients with T2N0 squamous carcinoma of the vocal cord to standard fractionation (70 Gy in 35 fractions) versus a hyperfractionated schedule (79.2 Gy in 1.2 Gy fractions delivered twice daily). Presented preliminary results which demonstrated a nonstatistically significant absolute local control advantage of ~10% in favor of the twice daily radiation arm,[84] which is comparable to the absolute local control gains in other trials and institutional series reporting altered fractionation outcomes versus standard fractionation.[76,85] However, results of RTOG 95-12 have not to date been fully published and have been long awaited.

Given the absence or scarcity of draining lymphatics from the true vocal cords, radiation treatment fields for stage I and the majority of stage II glottic cancers are limited to the larynx only (i.e., no “elective” lymph node/neck irradiation). This larynx-only radiation field has traditionally been delivered through mostly opposed lateral, slight anterior tilt, or wedge-pair low-energy (4 to 6 MV) photon fields (typical size 4 to 6 cm^2) commonly used with beam modifiers, such as photon attenuating wedges to improve dose homogeneity across the treatment volume, and surface bolus to ensure adequate dose to the AC when involved. These traditional field arrangements, while providing good coverage of the larynx, inherently lead to unnecessary radiation of the surrounding nontarget soft tissues of the neck and nearby carotid artery segments, which may have a long-term effect on producers on carotid atherosclerosis and subsequent cardiovascular events. Multiple studies have

investigated the technical feasibility of intensity-modulated radiation therapy (IMRT) technique to reduce dose to the carotid artery, particularly to the contralateral carotid artery in the setting of T1a disease. In general, IMRT produces more conformal dose distributions compared to traditional opposed lateral beam arrangements by applying multiple oblique beams of varying shape and intensity around the target in order to create geometrically complex dose distributions. Rosenthal and colleagues from the University of Texas MD Anderson Cancer Center conducted a dosimetric comparison study of traditional opposed lateral photon beam plans versus IMRT plans. IMRT plans provided comparable target volume coverage but significantly reduced intermediate and high doses to the carotid arteries compared to the traditional plans[86] (**Fig. 15.24**).

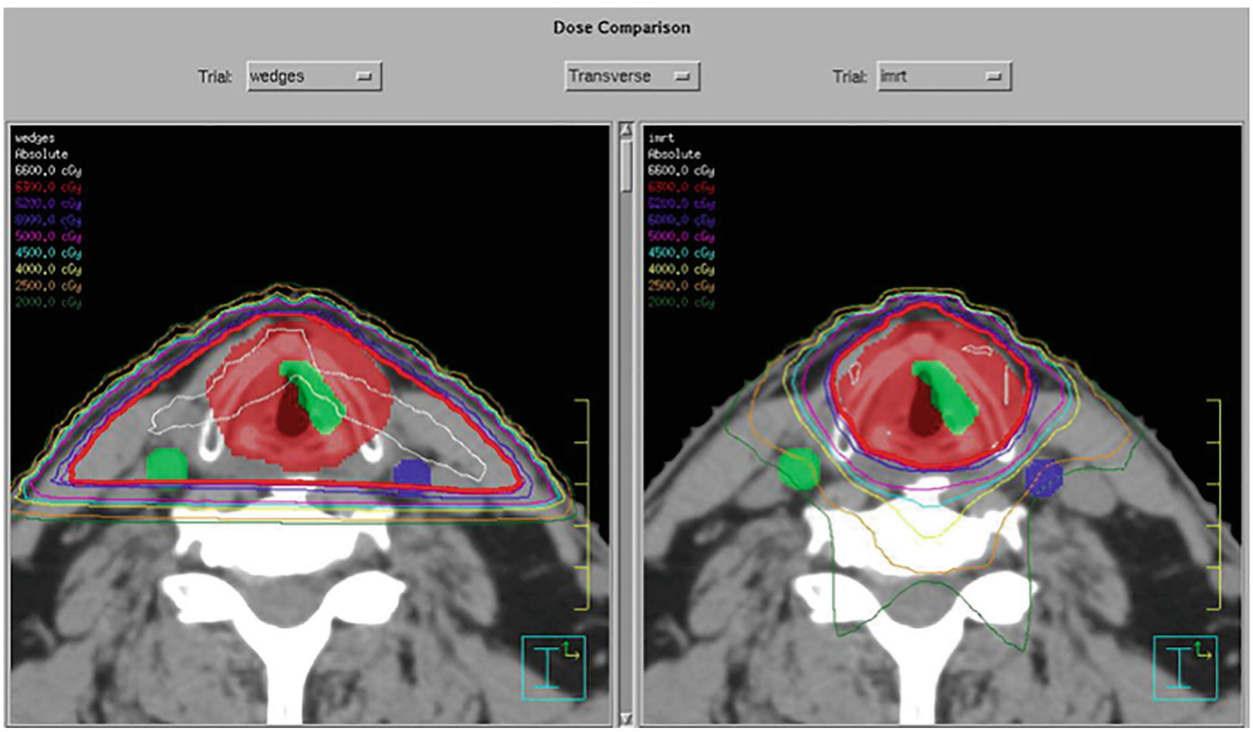

Figure 15.24. Stereotypic isodose plans for a traditional lateral field setup with wedges **(left panel)** and intensity-modulated radiotherapy (IMRT; **right panel**) for early glottic cancer (tumor in *green color* wash). Both plans demonstrate full coverage of primary target volume (shown in *red color* wash) by the 63 Gy prescription isodose line (*thick red line*), but the IMRT plan achieved target dose conformality resulting in sparing of adjacent carotid arteries from intermediate and high-dose distributions, with each carotid receiving <40 Gy in this case.

(Reproduced from Rosenthal DI, Fuller CD, Barker JL Jr, et al. Simple carotid-sparing intensity-modulated radiotherapy technique and preliminary experience for T1-2 glottic cancer. *Int J Radiat Oncol Biol Phys.* 2010;77(2): 455–461, with permission.)

Commonly used dose and fractionation regimens for T1N0 glottic larynx cancers in the United States include 66 Gy in 33 and 63 Gy in 29 fractions, with daily doses ≥2 Gy highly preferred. For T2N0 disease, accepted schedules include 70 Gy in 35 fractions delivered in 6 or 7 weeks, 74.4 to 79.2 Gy in 1.2 Gy twice daily fractions, or 65.5 Gy in 29 fractions. When concurrent chemoradiation is delivered for unfavorable T2N0 cancers, conventional fractionation to 70 Gy is preferred.

Advanced Glottic Cancer (Stage III and IV Disease)

The current standards for definitive radiation therapy–based treatment as an alternative to total laryngectomy for select patients with locoregionally advanced-stage cancer have been established through the serial execution of landmark clinical trials. The first of these, conducted by the Veterans Affairs Laryngeal Cancer Study Group, randomized patients with stage III/IV disease to surgery with postoperative radiation therapy versus induction chemotherapy followed by definitive radiation therapy for responders. Overall, larynx preservation was achieved in approximately two-thirds of patients, but nearly 60% of patients with full-thickness cartilage invasion required a salvage total laryngectomy. This trial demonstrated proof of principle that an attempt at larynx preservation was feasible for most patients without compromise in survival.[87] Building upon these results and excluding patients with full-thickness cartilage invasion and extensive involvement of the base of the tongue, the RTOG conducted a three-arm larynx preservation trial (RTOG 91-11) comparing induction chemotherapy followed by radiation therapy for responders, versus concurrent chemoradiation, versus radiation therapy alone. Long-term local control and larynx preservation rates were superior for those receiving concurrent chemoradiation compared to the other arms, but there was no statistically significant difference in overall survival between the groups. Teasing out detailed long-term laryngeal functional outcome differences in this trial has proven difficult,[88] but the increased number of deaths deemed unrelated to cancer that were observed in the concurrent chemoradiation arm has caused some to question the long-term toxicity of concurrent chemoradiation compared to radiation alone or

sequential chemoradiation.[89] Such deaths were more pronounced in elderly patients (older than 70 years). Generally, patients with more advanced local cancer (i.e., destructive T4 primaries) or poor laryngeal function at presentation (e.g., aspiration or poor airway protection) are best managed with surgery and postoperative radiation therapy or chemoradiation for the presence of high-risk pathology features such as compromised surgical margins and/or extracapsular extension of lymph node metastases.[90]

When treating locally advanced cancer in the setting of larynx preservation, the radiation treatment volumes are extended to include the involved and at-risk draining cervical lymphatics, and three-dimensional radiation therapy techniques, including IMRT, are commonly used. Whether treating in the definitive or postoperative setting and particularly when the upper neck is part of the radiation target volume, IMRT has been preferred over conventional techniques due to the ability to conform doses around the targets and facilitate relative sparing of the adjacent parotid glands and thereby reduce long-term xerostomia consequently improving QOL. In the setting of concurrent chemoradiation, dose delivered to locally advanced gross cancer is typically 70 Gy in 33 to 35 fractions with lower “elective” doses delivered to surrounding soft tissue and lymph node regions at risk of harboring occult microscopic disease, and this is typically accomplished using a single integrated IMRT plan.

Cancer of the Supraglottic Larynx

Single-modality definite radiation therapy is an effective treatment option for favorable primary squamous carcinomas of the supraglottis. Investigators from the University of Florida reported low complication rates and 5-year local control rates of 100% and 86% following radiation therapy for T1 and T2 tumors, respectively.[91] In contrast to the typical treatment volumes described above for stage I/II glottis cancers, treatment volumes must include the at-risk draining lymphatics for supraglottic primaries of all T categories. For properly selected patients with more locoregionally advanced disease, combined modality therapy as an alternative to total laryngectomy is preferred as supported by the aforementioned larynx preservation trials. As for locally advanced glottic cancer, IMRT is a preferred technique for most supraglottic cancers due to its ability to spare the parotid. When designing IMRT target volumes and treatment fields for cancers of any larynx subsite,

radiation oncologists must take great care to account for patient set-up uncertainties, possible daily variations of target/larynx position in the neck, and larynx motion during treatment delivery, whether due to swallowing or respiration (**Fig. 15.25**).

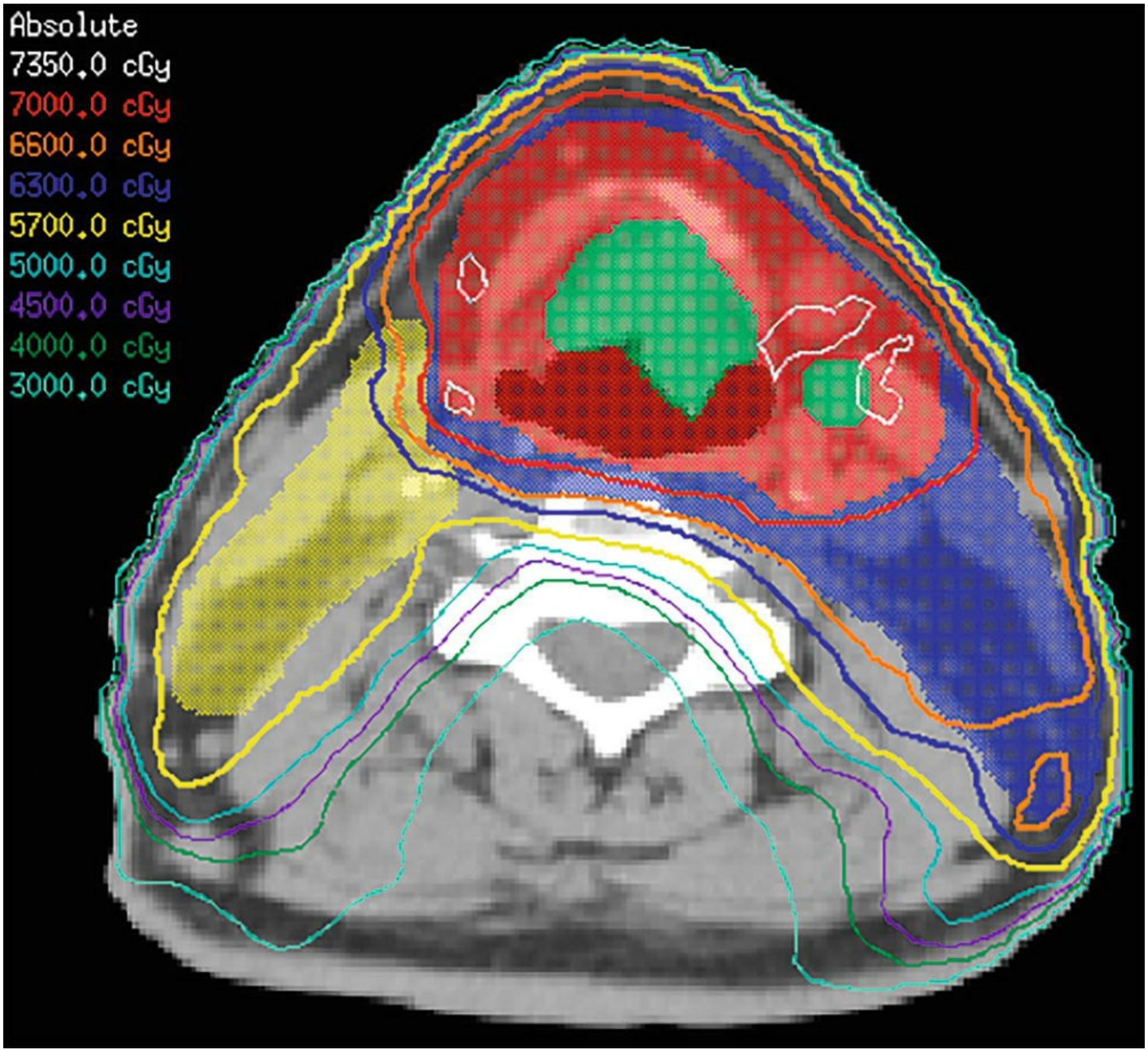

Figure 15.25. Representative axial CT image from IMRT treatment plan showing target volumes and accompanying isodose distributions for a 62-year-old male with left supraglottic squamous carcinoma, clinical stage T3N2bM0 treated with definitive concurrent chemoradiation. (*Green color wash* = gross primary tumor and adjacent positive lymph node; *red color wash* = 70 Gy high-risk treatment volume; *blue color wash* = 63 Gy intermediate-risk treatment volume; *yellow color wash* = 57 Gy standard-risk

treatment volume.)

Chemotherapy for Cancer of the Larynx

Though chemotherapy alone for cancer of the larynx is palliative, chemotherapy in combination with other treatment modalities can improve outcomes. Chemotherapy has been studied in multiple different settings—concurrently with radiation as definitive treatment, prior to definitive treatment as induction therapy, in the postoperative setting, and for palliation in patients with incurable recurrent or metastatic cancer.

Concurrent Chemoradiation for Cancer of the Larynx

In an attempt to improve cure rates and functional outcomes for patients with cancer of the larynx, the addition of chemotherapy to radiation therapy has been studied in multiple clinical trials.

RTOG trial 91-11 compared three treatments for locally advanced laryngeal cancer—radiation therapy alone, induction chemotherapy with cisplatin and fluorouracil followed by radiation, and concurrent chemoradiation with cisplatin, administered at 100 mg/m^2 on days 1, 22, and 43 of radiation therapy.[92] Though survival was not significantly different between the three arms, locoregional control and laryngeal preservation were superior in those receiving concurrent chemoradiation. Based on this data, concurrent chemoradiation with cisplatin became the standard of care for patients with good performance status and locally advanced cancer of the larynx.

Many other randomized trials have studied the combination of chemotherapy and radiation for cancer of the head and neck. The results of 93 randomized trials reported between 1994 and 2000 were summarized in the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MAHC-NC). In all of these trials, patients were randomized to receive either definitive local therapy (surgery or radiation) alone or with chemotherapy.[93] These trials enrolled some patients with cancer of the larynx, but also those with

cancer of the oral cavity, oropharynx, and hypopharynx. Patients receiving concurrent chemoradiation had a survival benefit of 8% at 5 years. Multiple different chemotherapy regimens were used; however, cisplatin appeared to be the most effective single agent.

Though high-dose cisplatin administered at 100 mg/m^2 IV every 3 weeks during radiation is considered the preferred standard for concurrent treatment, it is quite toxic and is best used in patients with a good performance status and without major comorbidities. Other schedules for cisplatin, including daily and weekly dosing, have been studied but have not been compared to high-dose cisplatin in a randomized trial.[94,95] Carboplatin has been studied as an alternative to cisplatin, as it has a lower risk of nephrotoxicity, ototoxicity, and neurotoxicity. Compared to radiation alone, concurrent treatment with a combination of carboplatin and 5-fluorouracil shows a survival benefit compared to radiation alone and is an acceptable regimen for patients who cannot tolerate cisplatin.[96]

Cetuximab, an anti-EGFR monoclonal antibody, has also been studied as concurrent treatment with radiation. In a randomized trial comparing cetuximab with radiation to radiation alone in stage III or IV cancer of the head and neck, cetuximab with radiation was superior to radiation alone in terms of overall survival and progression-free survival, though at the cost of increased toxicity.[97] About 25% of the patients enrolled in this trial had cancer of the larynx; the remainder had cancer of the hypopharynx or oropharynx. Concurrent cetuximab has not been compared directly with cisplatin for cancer of the larynx in a prospective trial; several retrospective series suggest inferior outcomes with concurrent cetuximab compared to concurrent cisplatin.[98,99] Cisplatin remains the standard of care for concurrent therapy for patients with locally advanced cancer of the larynx.

Induction Chemotherapy for Cancer of the Larynx

Induction chemotherapy has potential benefits over concurrent chemotherapy. Higher doses of chemotherapy can be used for induction rather than concurrent therapy, which may reduce the risk of distant metastases by treating micrometastatic disease before it becomes clinically apparent. It also may be better tolerated in some cases than concurrent therapy and can be used to select patients for organ preservation.[87] Data from

clinical trials, however, have not shown a definitive benefit for induction chemotherapy, and this approach remains controversial.

Induction chemotherapy has been studied as a way to select patients with cancer of the larynx for organ preservation approaches. In the VA Larynx Study, 332 patients with locally advanced squamous cell carcinoma of the larynx were randomized to receive either induction chemotherapy (cisplatin 100 mg/m^2 and fluorouracil 100 mg/m^2/day for 5 days every 3 weeks for two cycles) followed by radiation or surgery followed by radiation.[87] Patients assigned to the induction chemotherapy arm who did not respond to the first two cycles of chemotherapy underwent a laryngectomy. Disease-free survival and overall survival were not significantly different between the arms, and the larynx was preserved in 64% of patients receiving chemotherapy, demonstrating that induction chemotherapy could allow an organ preservation approach in the majority of patients without compromising outcomes compared to primary surgery. However, another trial from the GETTEC group with a similar design,[100] randomizing patients to primary laryngectomy versus induction chemotherapy followed by radiation therapy in responders, demonstrated inferior disease-free and overall survival in the induction chemotherapy group, with 2-year overall survival of 69% in the induction chemotherapy group and 84% in the laryngectomy group (p = 0.006).

As mentioned above, RTOG 91-11 compared induction chemotherapy followed by radiation, single-modality radiation, and concurrent chemoradiation.[92] A total of 547 patients were randomly assigned to receive radiation therapy alone, induction chemotherapy with cisplatin and fluorouracil followed by radiation, or radiation with concurrent cisplatin. Though overall survival was similar among all three groups, laryngeal preservation was significantly improved with concurrent therapy rather than either induction chemotherapy or radiation alone (84% vs. 72% vs. 67%). Toxicity was similar between the two chemotherapy arms and was increased compared to the radiation alone arm. Following the results of this trial, concurrent chemoradiation with cisplatin became the standard of care for locally advanced squamous cell carcinoma of the larynx, and the role of induction chemotherapy became less clear.

More recent induction trials have added taxanes to the traditional regimen of cisplatin and docetaxel. Induction with the TPF regimen (cisplatin,

docetaxel, and 5-fluorouracil) was shown to be superior to induction chemotherapy with cisplatin and 5-fluorouracil (PF) when followed by either radiation alone or radiation with carboplatin in the TAX 323 and TAX 324 studies.[101,102] Both of these trials enrolled patients with laryngeal cancer, in addition to patients with other primary sites, mainly oropharynx and hypopharynx.

Though studies show that TPF is a superior regimen to PF if induction chemotherapy is chosen, there are unanswered questions regarding induction chemotherapy. The optimal regimen for concurrent treatment following induction is not known, and it is also not known whether chemoradiation with concurrent cisplatin is superior to induction. There is significant disagreement in the head and neck community regarding the optimal role for induction chemotherapy—currently, it is not considered standard of care and should be performed in a tertiary care center with expertise in this area.

Adjuvant Chemoradiation Following Surgery for Cancer of the Larynx

For patients with adverse features, adjuvant radiation following surgical resection of laryngeal cancer is known to be beneficial.[103] Combinations of chemotherapy and radiation have also been studied in the adjuvant setting in two large trials, EORTC 22931 and RTOG 9501.[104,105] About 20% of the patients enrolled on these trials had cancer of the larynx; other sites including oral cavity were also well represented.

Patients with resected cancer of the head and neck with extracapsular extension, positive margins, or multiple involved lymph nodes were eligible for enrollment in RTOG 9501 and were randomized to either radiation alone or radiation with high-dose cisplatin (cisplatin 100 mg/m^2 on days 1, 22, and 43 of radiation therapy).[105] Patients who received chemotherapy had improved locoregional control and disease-free survival; however, overall survival was equivalent between the arms. EORTC 22931 used identical treatment regimens, but inclusion criteria were slightly different—eligible patients had T3 or T4 tumors or N2 or N3 cancer or other unfavorable features (extracapsular extension, positive margins, perineural involvement, or vascular tumor emboli).[104] This trial showed an improvement in progression-free as well as overall survival for the patients receiving

chemotherapy. Both trials showed that adding chemotherapy increased toxicity.

Results from these two trials were combined in an analysis to try to determine which patients might benefit from this approach.[90] Analysis showed that chemotherapy was of benefit in patients with extracapsular extension or positive margins; other patients did not have a clear benefit with the use of chemotherapy.

Currently, cisplatin combined with radiation therapy is the standard of care for patients with resected laryngeal cancer and positive margins or extracapsular extension. For patients with other high-risk features, concurrent chemotherapy can be considered, though the benefits are unproven. High-dose cisplatin is the preferred option; for patients who cannot tolerate high-dose cisplatin, weekly cisplatin or carboplatin-containing regimens can be considered.

Palliative Chemotherapy for Recurrent or Metastatic Cancer of the Larynx

For patients with cancer of the larynx who develop distant metastatic disease, or those who develop locally recurrent cancer not amenable to local therapy, chemotherapy is an option for palliation of disease. Chemotherapy can result in shrinkage of the cancer, improved control of symptoms, and possible prolongation of survival. Details of chemotherapeutic treatment for incurable head and neck squamous cell carcinoma will be discussed in another chapter.

Quality-of-Life Outcome

QOL outcome is very important in the formulation of treatment protocols. In a study from Europe, the QOL assessment included five treatment groups: cordectomy, PL, irradiation as primary therapy, laryngectomy, and combined laryngectomy and radiation therapy. Evaluation of the functional scales of the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C 30) revealed a higher QOL of patients with a maintained larynx compared with laryngectomies. On the symptom scales, patients after laryngectomy and/or radiation therapy suffered more

from fatigue, pain, and appetite loss. Laryngectomies stated enhanced financial difficulties. Evaluation of the ENT-specific EORTC module showed that patients after laryngectomy reported increased symptoms. Typical symptoms after radiation therapy included dry mouth, thickened secretions, and coughing.

Gourin et al. published a retrospective analysis of 2,370 cases using SEER Medicare data directed at assessing quality indicators of care for elderly patients with cancer of the larynx. Quality indicators were derived from the NCCN guidelines in addition to performance and end-of-life indicators. The authors noted that "high-quality" care in the primary treatment setting was associated with improvements in cost and survival; however, these findings were not seen when treating recurrence in this population. Patients treated with surgery and adjuvant radiation therapy demonstrated a potential survival advantage compared to individuals managed with nonoperative treatment in the review.[106]

Studies assessing QOL have demonstrated that patients with earlier-stage cancer of the larynx tend to feel they have better end organ function and QOL than individuals with more advanced-stage cancer after at 3 years after treatment. In patients with T1 disease, Robertson et al. showed no difference in QOL scores of T1 patients treated with primary radiation versus TLM. Their research did show that the mucosal injury associated with current chemoradiation techniques does translate negatively on the quality scores of patients later in life and their functional outcome.[107]

QOL after TLM was prospectively assessed in a study of 93 disease-free patients with predominantly early-stage glottic and supraglottic tumors. Speech was found to be the most important variable to 46% of patients within the study and voice quality was noted to improve for patients after treatment with TLM. Adjuvant radiation therapy and neck dissection were noted to be negative factors that independently impacted disease-specific QOL in the study population.[108]

Salvage Laryngeal Surgery

After treatment of locally advanced cancer of the larynx, some patients suffer

a local or regional failure that requires salvage surgery. The anatomic subsite in the head and neck where patients have the highest potential for successful surgical salvage is the larynx. Individuals with advanced-stage cancer of the larynx that recur after a organ-sparing chemoradiation protocol typically have disease extending to at least the boundaries of their pretreatment staging. As such, total laryngectomy is frequently required for salvage in these patients.[109]

Reynolds et al. reported on a prospective study that included 10 patients (5 supraglottic, 5 glottic) with T1/T2N0 cancer of the larynx that recurred after primary radiation therapy and were treated with transoral CO_2 laser salvage resection. Two patients required temporary tracheostomy and four required temporary gastrostomy tube placement. Local recurrence occurred in three patients after salvage surgery and two were salvaged with an open surgical procedure. The authors reiterate the theme that with careful patient selection, salvage endoscopic CO_2 resection for early-stage recurrent glottic and supraglottic tumors is a viable oncologic option.[110]

Endoscopic CO_2 laser surgery in the setting of recurrent cancer of the larynx can be challenging and requires appropriate patient selection. In a review of 11 articles by Ramakrishnan et al., the local control rate at 2 years for 249 patients after initial transoral laser microsurgical salvage procedure was 56.9%. For those capable of undergoing subsequent endoscopic re-resection, this number rose to 63.8%. The pooled mean laryngeal preservation among the studies reviewed was 72.3%. The majority of patients were initially clinically T1 (67%) and T2 (20.5%). The authors did note that the reported oncologic outcomes of open partial laryngectomy were superior to the findings of their review of endoscopic salvage. Endoscopic salvage for recurrent AC involvement was considered the least likely presentation to result in successful retreatment for cure and may be unsuitable for the transoral laser microsurgery approach.[111]

Salvage surgery was assessed in a review of 75 patients with recurrence of early (T1/T2) cancer of the glottis, treated previously with radiation therapy. The authors found that over 50% of patients were upstaged at the time of recurrence compared to their original pretreatment staging, with 39% of patients having cancer consistent with T3/T4 staging at recurrence. Only 16% of patients were considered candidates for salvage partial laryngectomy

with the remainder requiring total laryngectomy. The restaging of the patient's cancer at the time of recurrence was found to be the only prognostic factor associated with overall survival ($p = 0.004$).[112]

Hong et al. reported on their experience with salvage endoscopic CO_2 laser resection for recurrent supraglottic carcinoma in a series of seven patients (2 T1, 2 T2, 3 T3). One patient experienced recurrence requiring salvage total laryngectomy. Contraindications to endoscopic salvage in their group included cricoid, hyoid, or thyroid cartilage invasion, cardiopulmonary dysfunction, extensive preepiglottic spread, and vocal cord fixation. Salvage neck dissection was performed simultaneously with endoscopic resection. The majority of patients (6/7) required a tracheostomy at the time of surgery and had a mean time to decannulation of 10.7 days. Fixation of the vocal cord was experienced as a complication by two patients. Oral feeding was initiated in all patients by postoperative day 3. The 5-year overall survival for the group was 68.6%. The authors commented that endoscopic salvage of selected recurrent T3 cancers of the supraglottis was possible when preepiglottic space extension was limited.[113]

Short-term implications of postlaryngectomy fistula formation include prolonged hospitalization, increased cost of care, and a potential delay in the initiation of adjuvant care. Long-term complications of fistula formation include dysphagia, stricture, and prolonged dependence on gastrostomy tube assistance for nutrition. Use of the pectoralis major flap or free-tissue transfers after salvage laryngectomy have been suggested for the ability to decrease the severity and shorten the length of time to resolution of postoperative fistula versus primary closure in the postradiation setting.

As a follow-up to the RTOG 91-11 organ preservation trial, Weber et al. reviewed the incidence of complications experienced with salvage total laryngectomy following induction chemotherapy followed by radiation, CRT, and radiation alone. Of the 517 patients originally enrolled, 129 ultimately required salvage laryngectomy, with 5% of patients requiring salvage for the indication of aspiration and necrosis of the larynx. The incidence of minor (self-limited and did not extend hospitalization) and major (prolonged admission and were life threatening) complications varied between 52% and 59% in the three arms. The rate of postoperative fistula ranged from 15% (radiation alone) to 30% (concomitant CRT). The incidence of fistula was independent of the timing of salvage laryngectomy relative to prior primary

therapy. The mortality rate of surgical salvage was low with only one perioperative death occurring from myocardial infarction. The 2-year survival rate for patients requiring salvage laryngectomy was 72%.[114]

In one study, individuals who underwent salvage laryngectomy (partial and total) had a reported locoregional control rate of 70%. Open partial laryngectomy options, including VPL and supracricoid laryngectomy, were predominantly used in patients with early-stage recurrence. Contraindications to partial laryngectomy in the study included preepiglottic space invasion, interarytenoid extension, arytenoid fixation, and extralaryngeal extension of cancer. Total laryngectomy, the most common procedure used in the series of 100 patients, was performed in 66.6% with early-stage recurrence and in 85.7% with advanced-stage recurrence. Of note, tumor staging (initial or recurrent), type of salvage treatment, and cervical lymph node metastases did not demonstrate a statistical impact on survival. Most of the patients within the series developed recurrent cancer within 11 to 15 months after the completion of primary therapy, which re-emphasizes the importance of close clinical follow-up in the first 2 years after treatment. The authors also suggested that neck dissection should be strongly considered at the time of salvage surgery given that nearly one-third of patients in their series who underwent neck dissection harbored regional metastases on final histopathology.[115]

Sayles et al. performed a review of 171 patients to determine the fistula rate of patients after undergoing salvage laryngectomy after organ preservation therapy versus those undergoing primary surgical management. The fistula rate for the entire study population was 29%. Individuals undergoing salvage laryngectomy after radiation +/− chemotherapy experienced a statistically significant increase in the development of postoperative fistula (37.3% vs. 17.0%, $p = 0.03$) than individuals undergoing primary laryngectomy. As a result of their findings, the authors suggested the use of vascularized tissue flaps to reduce the rate of fistula incidence and severity in individuals requiring salvage surgery.[116]

In a review comparing pectoralis flaps, myofascial overlay versus myocutaneous (integrated into pharyngeal closure), in patients undergoing salvage laryngectomy after radiation therapy (37.5% CRT), fistula rates associated with the two forms of reconstruction were compared. The difference in fistula rates between the two groups was not found to be

statistically significant (myofascial overlay 26.3%, myocutaneous 33.3%). As a result, the authors suggest the use of the pectoralis myofascial overlay flap when the use of a skin paddle is unnecessary for adequate pharyngeal closure.[117]

Stomal Recurrence

Stomal recurrence refers to a local recurrence arising from the margins of the tracheal or pharyngeal resection in the peristomal area, after a total laryngectomy. This disappointing result has a poor associated prognosis, yet surgical salvage can be offered in selected situations versus radiation/reirradiation or palliative chemotherapy.

Classification

The classification system of Sisson and colleagues[118] describes in the following ways the location of the recurrent cancer for the purposes of staging and prognosis:

Type I-cancer involves the superior half of the stoma without esophageal involvement.

Type II-cancer involves the superior half of the stoma with esophageal involvement.

Type III-cancer involves the inferior half of the stoma and extends into the mediastinum.

Type IV-cancer extends out laterally underneath the clavicles.

Incidence

In their comprehensive review of references encompassing 4,281 laryngectomies, Esteban and coworkers calculated the overall incidence of stomal recurrence to be 6%. Of the many risk factors identified, subglottic extension of the cancer is the one factor unanimously agreed upon as a significant risk.[119] Rubin et al.[120] studied line-independent variables with multivariate analysis and found that cancer involving the subglottis and the size of the primary cancer (stage T4) were the only significant predictors of

stomal recurrence.

Concerns have existed for an increased risk of stomal recurrence after laryngectomy when preceded by emergent tracheotomy because of the hypothetical possibility of cancer “seeding” into the trachea and peristomal soft tissues. Some have even endorsed the idea of “emergency laryngectomy,” performed in the same setting as the tracheotomy for the obstructing cancer, to help prevent stomal recurrence. However, studies have failed to show previous tracheotomy to be an independent risk factor. A study of 444 laryngectomy patients found no difference in stomal recurrence rate among the subglottic cancers that required emergent tracheotomy.[120] The authors proposed that the size and location of cancer of the subglottis made it more prone to both stomal recurrence and the need for urgent tracheotomy and that the tracheotomy itself was not an independent risk factor.

Management

The management of stomal recurrence is primarily surgical. Currently, mediastinal dissection is recommended for type I and type II stomal recurrence with possible postoperative radiation. Patients with type III and type IV disease can be offered surgery if they are medically fit and are willing to accept higher morbidity and mortality rates. Radiation therapy has been reported to provide palliation but is ineffective when used as a single agent. Furthermore, many patients have already had full-course radiation to control their primary cancer and are not able to receive further therapeutic doses. Combinations of radiation and chemotherapy when feasible have been used with encouraging early results.

Surgery includes resection of the tracheostoma and the surrounding skin, mediastinal dissection with removal of the manubrium (with or without removal of the heads of the clavicles), and resection of involved pharyngoesophageal segments with reconstruction and obliteration of dead space using various flaps (**Figs. 15.26 and 15.27**). Perioperative mortality approaches 15%, and death most often results from mediastinitis and rupture of the great vessels. Gluckman and coworkers reported the results of 41 mediastinal dissections for stomal recurrence of all types. Overall survival was a dismal 16% with a 24% determinate survival rate. Survival among type I and II lesions was 45%, but among types III and IV, it was only 9%. Acceptable palliation of pain and airway obstruction was achieved in the

nonsurvivors.[121]

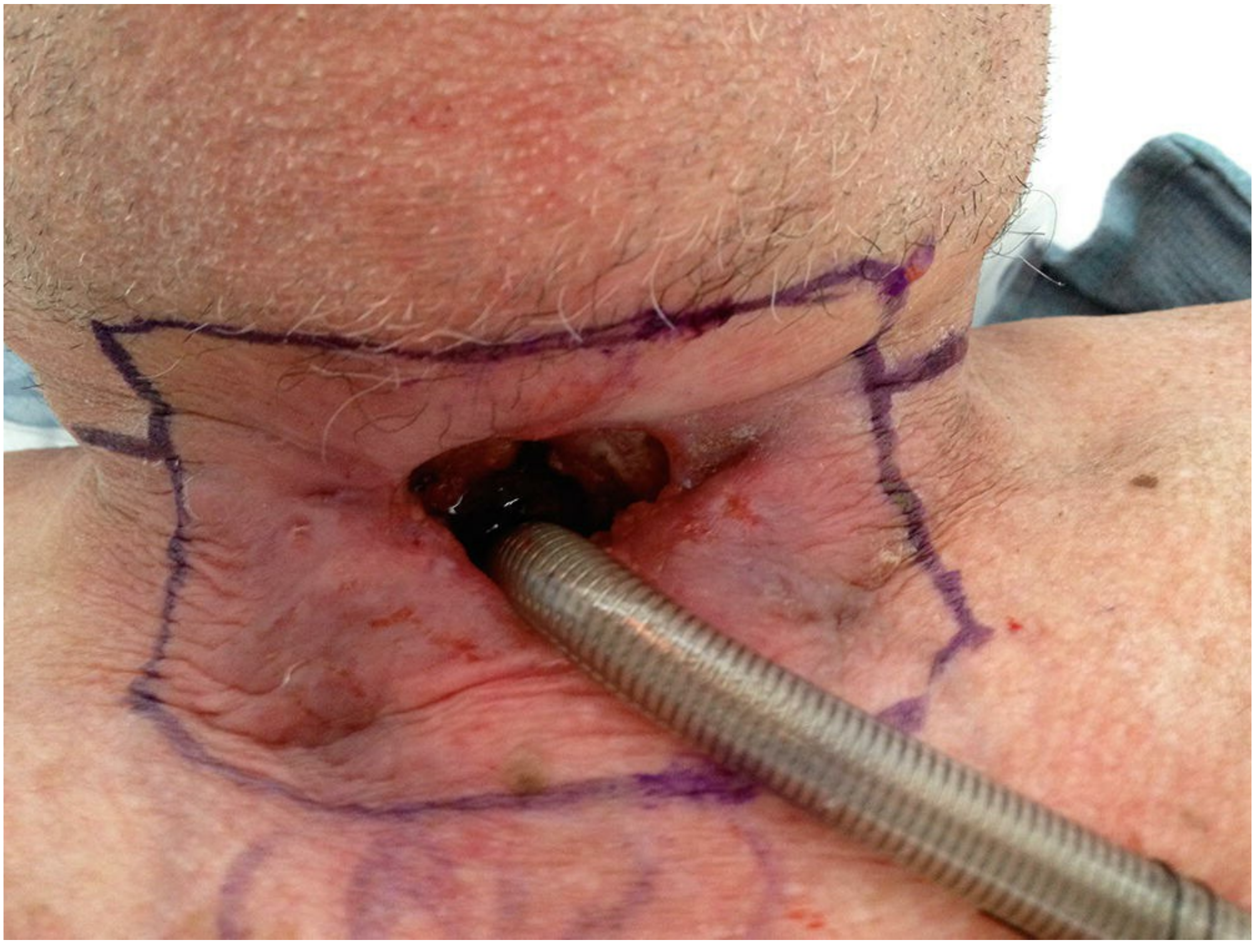

Figure 15.26. Stomal recurrence after laryngectomy with marking for planned resection.

Figure 15.27. Postoperative view after salvage resection for peristomal recurrence with pectoralis major flap reconstruction of the anterior neck and superior “neostoma.”

Pet Scanning in Posttreatment Evaluation

With regard to local response, Brouwer et al. reviewed 30 patients suspected of having recurrent cancer of the larynx after radiotherapy who underwent PET and direct laryngoscopy with biopsy. Recurrence was diagnosed by biopsy in 8/30 patients. Sensitivity and specificity of PET were 88% and 82%, respectively. The authors noted that, among radiologists involved in the study, the interobserver agreement and variability seen in the study were reasonable and suggested that PET represented an option to operative biopsy

to assess patients for recurrence.[122] The cost-effectiveness of PET in the selection of patients for operative biopsy with suspected recurrent laryngeal carcinoma after radiotherapy was reviewed by van Hooren et al. The direct medical costs of 30 patients comparing an approach where all patients underwent direct laryngoscopy was compared to a PET strategy in which only patients with a positive or equivocal PET underwent direct laryngoscopy. The mean cost of the PET-based strategy was noted to cost 399 Euros less than the empiric direct laryngoscopy strategy.[123]

In assessing the need for regional salvage, Gilbert et al. reviewed the ability of preoperative PET–CT (15 patients) to predict the pathologic status of the neck in N0 patients with locally recurrent cancer of the larynx. In this series, three patients with clinically N0 necks and negative PET–CT had positive pathology in the lymph nodes, resulting in a sensitivity of 70% and an NPV of 62.5%. The authors felt that the false-negative rate warranted recommending clinically N0 patients with recurrent cancer of the larynx be offered neck dissection at the time of salvage laryngectomy independent of preprocedure PET–CT results.[124] Gourin et al. reviewed 32 patients with N2/N3 cancer that experienced a complete clinical response after CRT underwent PET–CT 8 to 11 weeks after treatment to assess the ability of the imaging technique to predict the need for staged neck dissection. PET–CT was considered positive in 20 patients (63%). Final pathology revealed viable carcinoma in 10 of the 32 neck dissections. Only 6 of the 20 PET–CT positive scans correlated with a positive neck dissection, whereas 4 of 12 negative PET–CT scans were associated with persistent regional metastases. The sensitivity and specificity of PET–CT were 60% and 36%, respectively. The authors concluded that PET–CT does not reliably predict the need for planned posttreatment neck dissection in patients with a complete clinical response following CRT. Their data also suggested that delaying the timing of PET–CT beyond 8 to 11 weeks, with surgery reserved for positive findings, could be a reasonable alternative to empiric neck dissection.[125]

Treatment of the Neck

Surgical Treatment of the Neck in Cancer of the Larynx

Debate exists regarding the management of the clinically negative and positive neck in cancer of the larynx. Elective treatment of the neck is recommended for supraglottic cancers staged T2 or higher and for glottic or subglottic tumors staged T3 or higher. The neck may be treated electively by either surgery or radiation, with radiation employed for cases in which that modality is employed for the primary cancer.

Elective neck dissection provides important information for prognostic purposes and therapeutic decisions by establishing the presence, number, location, and nature of occult lymph node metastases. Selective lateral neck dissection (levels II, III, and IV), unilateral or bilateral, is the procedure of choice for elective treatment. Paratracheal nodes (level VI) should be dissected in cases of advanced glottic and subglottic cancer. Complete radical or functional neck dissections are often excessive in extent in that levels I and V are rarely involved. Sentinel lymph node biopsy procedures have not been shown to be effective for primary cancer of the larynx. The clinically involved neck is usually treated by a functional neck dissection of levels I through V or MRND/RND as indicated.

Selective neck dissection has been employed successfully in selected cases, particularly for N1 or occasionally N2 nodal involvement. Selective neck dissection can be extended to include structures at risk. More advanced cancer has been treated in this manner, often in association with adjuvant chemotherapy and/or irradiation. Although the benefit of adjuvant treatment is difficult to assess, it appears most useful in cases with extracapsular spread —a feature associated with the worst prognosis.

Either modified type III radical neck dissection (MRND) or lateral neck dissection (LND) is considered valid treatment for patients with cancer of the larynx with clinically negative neck findings (N0) who are undergoing surgical management of the primary. A prospective study was performed to compare complications, neck recurrences, and survival results of elective MRND and LND on the management of laryngeal cancer patients. A total of 132 patients were included in the trial. All patients had previously untreated T2–T4 N0M0 supraglottic or transglottic SCC. Seventy-one patients underwent MRND (13 bilateral) and 61 underwent LND (18 bilateral). The rate of occult metastasis detected on histologic examination was 26%, and most positive nodes occurred at levels II and III.[126]

Treatment of the Neck in Cancer of the Supraglottis Cancer

The role and extent of neck dissection after definitive radiation therapy in patients with cancer of the supraglottis specifically for N0 and N1 disease is controversial. Regional response has been related to the size of the lymph nodes at presentation. Most patients with nodal size of 3 cm or less had a complete response, whereas patients with nodal size >3 cm had a partial response. For patients with a complete response in whom postradiation therapy neck dissection was withheld, regional control rates were 75% and 86% for N1 and N2, respectively. In multivariate analysis, significant favorable factors predictive for regional control were female sex, accelerated hyperfractionation, and complete response; factors predictive for overall survival were Karnofsky Performance Scale score and regional response. Isolated regional relapse is not common among patients with cancer of the supraglottis when a complete response is achieved at 4 to 6 weeks after definitive radiation therapy is provided and postradiation therapy neck dissection is not performed.[127]

Outcomes Research

As part of a larger project, 597 patients with laryngeal carcinoma had data abstraction performed relative to their survival and functional outcomes at MD Anderson Cancer Center. Overall survival at 1- and 2-year posttreatment was 93% and 87%, respectively. Tier 1 outcomes at 1 year for tracheostomy-free and feeding tube-free status were 96% and 90%, respectively. Tracheostomy-free status correlated with the capacity for functional speech production.[128]

Sandulache et al. reported the Veterans Affair Medical Center (VAMC) experience with laryngeal cancer in their review of 205 patients treated over a 12-year period. They reported an overall 2-year DFS of 68% and OS of 74%. The cohort of patients seen at the Michael E. DeBakey VAMC was predominantly early-stage glottic and advanced-stage supraglottic primaries with regional spread. As would be expected, the 2-year DFS and OS for glottic (72%, 77%) was better than for cancer of the supraglottis (63%, 69%). The authors cited their high compliance with the NCCN guidelines as a factor

associated their favorable oncologic outcomes. The rate of second cancers in the series was high at 21%, with the majority of these being cancers of the lung. Additionally, 97% of this group reported a history of tobacco use. There was no difference observed in DFS or OS between black and white male patients treated during this time frame leading the authors to suggest that when access to care is equal, outcomes should be similar independent of race.[129]

In a multicenter, retrospective review of 234 patients with early glottic carcinoma, Kerr et al. compared TLM (143) versus radiation therapy (91) in voice outcomes and laryngeal preservation rates. The 2-year organ preservation rates for stage 1 disease for TLM and radiation therapy were 100% and 92%, respectively ($p < 0.004$), whereas in rates for stage 2 disease, there was no significant difference. The VHI-10 scores favored radiation therapy at all time points when compared to TLM.[130]

Summary

The treatment of cancer of the larynx is dependent upon the anatomical location and stage of the presenting lesion. In addition to purely oncologic considerations, the preservation of QOL metrics helps drive decisions in the primary management of these patients. Early-stage cancers may be considered for single modality therapy whereas advanced-stage cancers frequently require combination chemoradiation or surgery with adjuvant radiation therapy. Prospective multidisciplinary management of laryngeal cancer affords patients the best available oncologic and functional outcomes.

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16 Cancer of the Hypopharynx and Cervical Esophagus

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Cancer of the hypopharynx and cervical esophagus often present significant challenges in management, owing to the critical role these anatomical sites play in the normal function of the upper aerodigestive tract (UADT). The structural proximity, close physiologic coordination, and similarity in oncologic aspects allow concurrent discussion of cancer arising from the two sites. Treatment of cancer of the hypopharynx and cervical esophagus includes the use of surgery, radiotherapy, and chemotherapy in different combinations depending upon the stage of the cancer. With a growing emphasis on organ preservation, the selection of therapeutic option, surgical or nonsurgical, which maximally controls disease and preserves function, remains critical. This chapter focuses on the approaches to the management of cancers of the hypopharynx and cervical esophagus with relevant anatomic, pathologic, and etiologic details.

Surgical Anatomy

The hypopharynx extends from its junction with the oropharynx at the level of the tip of the epiglottis to its junction with the cervical esophagus inferiorly (**Fig. 16.1**). The bony landmarks are the hyoid superiorly, the lower border of the cricoid cartilage inferiorly, and C3 to C6 vertebrae posteriorly. The hypopharynx is comprised of three anatomical subsites—the pyriform sinus (PFS), the postcricoid area, and the posterior pharyngeal wall. These three subsites are continuous with one another and cancers often involve more than one subsite.

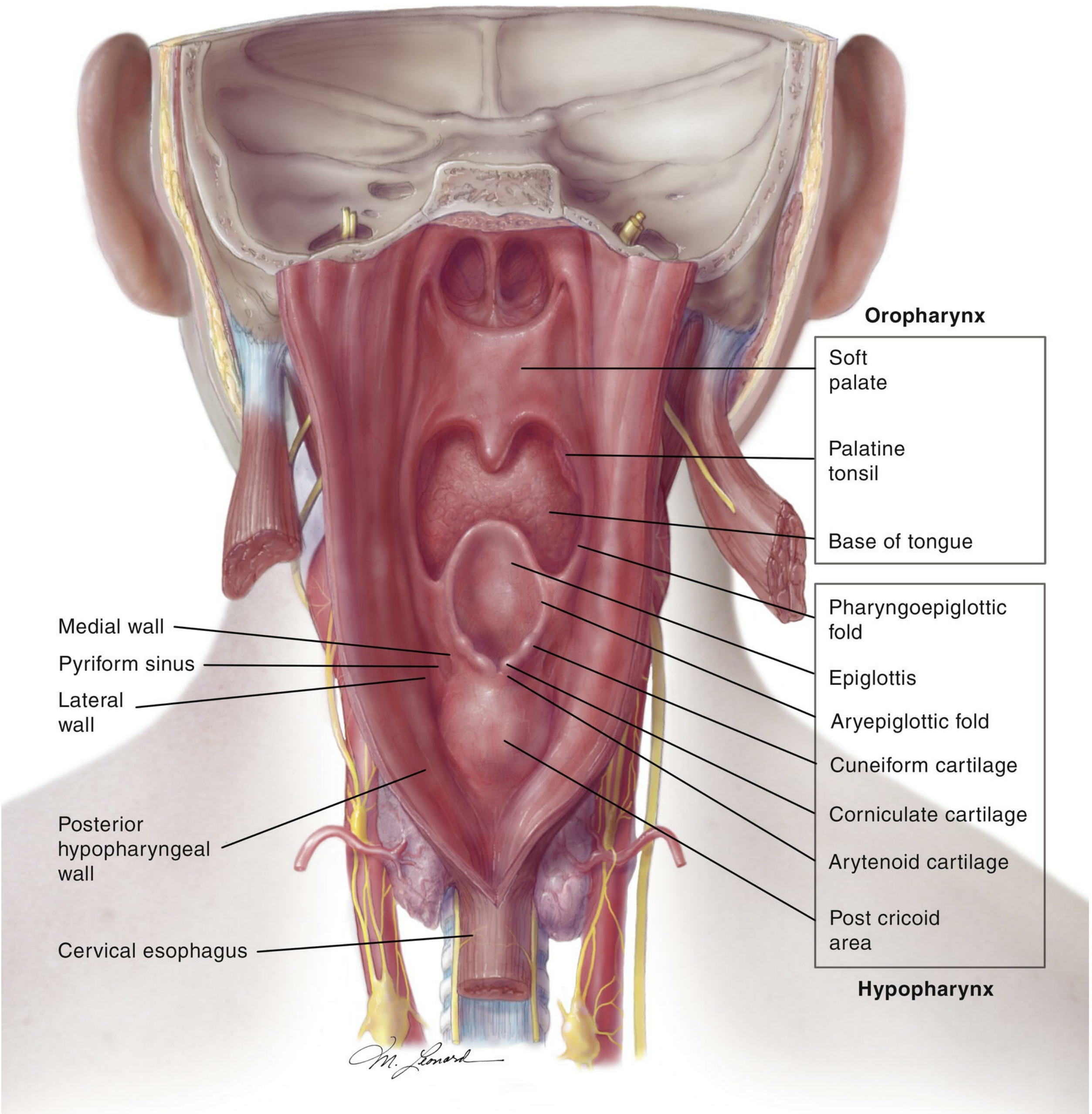


Figure 16.1. Anatomical subdivisions of the pharynx (posterior view).

The PFS is a conical structure located on each side of the hypopharynx that extends from the pharyngoepiglottic fold down to its inferior-most extent, the apex, which opens medially into the cervical esophagus. The superior part of the PFS is bounded by the thyrohyoid membrane and thyroid cartilage laterally and the aryepiglottic fold (AEF) and arytenoid cartilage medially. The apex of the PFS is bounded by the thyroid cartilage laterally and by the cricoid cartilage medially. The medial wall of the PFS is separated from the

endolarynx by the AEFs.

The postcricoid area extends from the level of the arytenoid cartilages to the inferior border of the cricoid cartilage at the pharyngoesophageal junction. It lies in close proximity to the posterior cricoarytenoid muscles and the medial wall and apices of the PFSs.

The posterior wall of the hypopharynx extends from the level of the tip of the epiglottis (or the floor of the vallecula) to the level of the inferior border of the cricoid cartilage. The superior and inferior boundaries of the posterior wall of the hypopharynx merge with the walls of the oropharynx and the esophagus, respectively, whereas the lateral boundaries are continuous with the PFS. The mucosal lining of the wall of the hypopharynx is separated from the prevertebral space by a fibrous layer formed by the pharyngeal aponeurosis; a muscular layer formed by the middle and inferior constrictors; the buccopharyngeal fascia; the retropharyngeal space; and the prevertebral fascia. The distal-most fibers of the inferior constrictor muscles form the cricopharyngeus muscle, which constitutes the primary muscle of the upper esophageal sphincter and marks the junction between the postcricoid area and the cervical esophagus.

The cervical esophagus lies posterior to the trachea and thyroid gland, extending from the inferior border of the cricoid cartilage (opposite C6 vertebra) to the level of the thoracic inlet (opposite T1 vertebra). It deviates to the left in the inferior aspect of the neck and is medial to the common carotid artery and recurrent laryngeal nerve on either side and the thoracic duct on the left. The esophageal wall from inside out is made up of a mucosal, submucosal, muscular, and an external fibrous layer. The muscular layer consists of internal circular fibers, which are continuous with the cricopharyngeus muscle, and external longitudinal fibers that are covered with a fibrous layer in continuity with the wall of the hypopharynx.

Nerve supply: The pharyngeal constrictor muscles receive motor innervation through the pharyngeal plexus with additional innervation of the inferior constrictors from branches of the external laryngeal and the recurrent laryngeal nerves. The recurrent laryngeal nerve provides motor innervation to the cricopharyngeus and the posterior cricoarytenoid muscles, whereas the sensory innervation of the hypopharynx is derived primarily from the internal branch of the superior laryngeal nerve. This branch synapses with a branch of the vagus, Arnold’s nerve, which provides sensation to the external auditory

canal and which accounts for the symptom of referred otalgia from cancer of the hypopharynx. Additional sensory innervation is also provided by branches of the recurrent laryngeal nerve. Innervation to the cervical esophagus is derived from the recurrent laryngeal nerve and sympathetic chain.

Vascular supply: The superior laryngeal branch of the superior thyroid artery is the primary blood supply to the superior aspect of the hypopharynx; the inferior part is supplied by the inferior laryngeal branch of the inferior thyroid artery. The vascular supply of the cervical esophagus is derived primarily from the inferior thyroid artery. Venous drainage from the hypopharynx occurs through the submucosal pharyngeal venous plexus, which drains into the internal jugular vein, whereas the cervical esophagus drains into the inferior thyroid vein.

Lymphatic drainage: The hypopharynx is rich in lymphatics, which pierce the thyrohyoid membrane to drain into the deep jugular chain (level II, III, and IV) nodes. Lymphatics from the inferior aspect of the PFS and the postcricoid area pierce the cricothyroid membrane and drain into the paratracheal chain (level VI) nodes. From the posterior pharyngeal wall, drainage occurs into the retropharyngeal nodes (RPLNs) including the nodes of Rouviere superiorly. Lymphatics from the cervical esophagus usually drain first into the paratracheal and paraesophageal nodes, and second, into the cervical and superior mediastinal nodes.

Patterns of Spread

Cancers from the medial wall of the PFS spread medially to the endolarynx by invading the AEF or the paraglottic space causing fixation of the hemilarynx. Posterior extension into the postcricoid area can lead to infiltration into the posterior cricoarytenoid muscle with fixation of the ipsilateral vocal cord. Infrequently, fixation of the hemilarynx can also result from the direct invasion of the cricoarytenoid joint or the recurrent laryngeal nerve. Anterior and lateral spread leads to involvement of the lateral wall of the PFS and/or the wall of the hypopharynx. From the lateral wall of the PFS, cancer can extend into the cervical soft tissues to involve the strap muscles, thyroid gland, and other extralaryngeal structures through direct invasion of

the thyroid cartilage or by spread around the posterior border of the thyroid cartilage at the insertion of the inferior constrictor muscles. Posterior extension involves the posterior wall of the hypopharynx, whereas the lateral wall of the oropharynx, pharyngoepiglottic fold, and the base of the tongue can be involved by superior extension. Cancers reaching the apex of the PFS can involve directly the postcricoid area and the cricoid cartilage.

Cancers of the postcricoid area can extend directly to the cricoid cartilage and the trachea and, submucosally, toward the cervical esophagus. Submucosal spread of cancer superiorly to the oropharynx and inferiorly to the esophagus can also occur from the posterior wall of the hypopharynx. Cancers from this site can involve the pharyngeal constrictors and the buccopharyngeal fascia. The fascia is a weak barrier, and further posterior spread can involve the prevertebral fascia and the prevertebral musculature, ultimately reaching the periosteum of the vertebral column.

Cancers of the cervical esophagus can spread anteriorly to the trachea, laterally to the tracheoesophageal groove and recurrent laryngeal nerve(s), and posteriorly to the prevertebral space.

Epidemiology

Cancer of the hypopharynx is rare and accounts for 3% to 5% of the malignancies in the UADT.[1] The American Cancer Society estimates 3,400 cases in 2014, ~2,725 in men and 675 in women. The worldwide age-standardized incidence estimated by GLOBOCAN 2012 report from the International Agency for Research on Cancer (IARC) is 1.9 per 100,000 and a total number of 142,387 new cases.[2] The precise incidence for either the hypopharynx or the individual hypopharyngeal subsites is, however, difficult to estimate due to the combined reporting on all cancers of the pharynx by the IARC. In addition, a marked gender and geographical variation is known to exist, with a higher incidence in males and in certain regions of Central and Eastern Europe, France, and Southeast Asia.

Cancer of the PFS and posterior hypopharyngeal wall occurs predominantly in males, aged 55 to 70 years, and is strongly associated with excessive alcohol consumption and smoking. Carcinoma of the postcricoid

area is more common in females, aged 30 to 50, with underlying nutritional factors such as Plummer-Vinson syndrome as a possible etiology. It is mainly reported from Sweden and other Scandinavian nations; however, improved nutrition has been shown to decrease the incidence of Plummer-Vinson syndrome and, therefore, the incidence of postcricoid carcinoma from these regions.[3,4] Chronic gastroesophageal reflux and human papillomaviruses are postulated to have an etiologic association to cancer of the hypopharynx in nonsmokers and nondrinkers.[5] Genetic predisposition and occupational exposure to carcinogens such as solvents, polycyclic aromatic hydrocarbons, sulfuric acid, asbestos, welding fumes, wood dust, nickel, and leather have also been implicated as etiologic factors.[3]

Cancers involving the cervical esophagus make up 2% to 10% of all cancers of the esophagus and are derived from the caudal extension of cancers originating in the hypopharynx.[6,7] Cervical esophageal cancer is predominantly seen in males and has a high incidence in certain regions of Iran, Central Asia, Mongolia, and Northern China. The risk factors for the development of cancer of the cervical esophagus are similar to those for the hypopharynx. Prolonged irritation from thermal injury or corrosives such as lye is also associated with increased risk.

Histopathology

Approximately 95% of the cancers of the hypopharynx and cervical esophagus are squamous cell carcinomas (SCC). Invasive SCC may be preceded by premalignant lesions. The PFS is the most common site of involvement, accounting for 65% to 85% of the hypopharyngeal SCC, followed by the posterior wall of the hypopharynx (10% to 20%) and the postcricoid area (5% to 15%). Submucosal spread and skip lesions are an important characteristic of cancers arising from these sites; spread of 5 to 30 mm beyond macroscopically visible cancer has been observed.[8] Whereas cancers of the PFS and posterior pharyngeal wall are more frequently exophytic, postcricoid cancers are more commonly ulcerative. Basaloid carcinoma, undifferentiated carcinoma, and spindle cell carcinoma are rare SCC variants characterized by more aggressive behaviors.[9] Spindle cell carcinoma occurs mostly in patients with a history of prior radiation that

typically presents as a polypoid mass projecting into the pharyngeal lumen.[10] The hypopharynx and cervical esophagus can also give rise to malignant nonsquamous tumors such as, (1) minor salivary gland adenocarcinoma and adenoid cystic carcinoma; (2) sarcomatous lesions such as fibrosarcoma, leiomyosarcoma, liposarcoma, and synovial cell sarcoma; (3) reticuloendothelial tumors such as lymphoma and plasmacytoma; and (4) melanoma.

Tumor Biology

Site-specific chromosomal aberrations are not so well defined in carcinomas of the head and neck; however, 11q13 amplification and loss of p53 heterozygosity have been reported in 78% and 70% of hypopharyngeal SCCs, respectively. The presence of 11q13 amplification has been associated with nodal metastases, greater local aggressiveness, and higher recurrence rates.[11] A loss of chromosome 18 has also been observed in 57% of cancers of the hypopharynx.[12]

Clinical Presentation and Evaluation

Presenting Symptoms and History

The common presenting symptoms, which suggest cancers originating from the hypopharynx and cervical esophagus, are progressive dysphagia, odynophagia, sore throat, referred otalgia, weight loss, and/or a mass in the neck. These cancers usually present at an advanced stage because the nonspecific symptoms of minor irritative sensation or sore throat from early-stage cancer may be too easily dismissed. Aspiration, hemoptysis, and weight loss occur with advanced cancer. Persistent pain in the throat with referred otalgia may be indicative of perineural invasion. Hoarseness and breathing difficulty are indicative of laryngeal involvement. Metastases to the cervical lymph nodes are known to occur in 50% to 80% of the patients at

presentation, and not infrequently, patients may present with only a metastatic mass in the neck in the absence of any of the aforementioned symptoms related to the primary cancer.[1,13] A thorough history should be elicited about prior risk factors including alcohol and smoking habits, laryngopharyngeal or gastroesophageal reflux, nutritional status, Plummer-Vinson syndrome, and occupational exposures; past treatments such as radiation and/or chemotherapy; and general medical condition including coexisting pulmonary or cardiovascular comorbidities.

Physical Examination

A complete examination of the head and neck including an indirect or fiberoptic laryngoscopy to evaluate the pharynx and larynx is the first step in the diagnostic evaluation. The site and extent of the cancer, vocal cord mobility, airway patency, and mobility and appearance of the arytenoids are assessed. Maneuvers such as phonation and/or Valsalva with a pinched nose offer better visualization of the PFSs with fiberoptic endoscopy. In the absence of a frank mass or surface ulceration, findings of pooling of saliva in the PFS, an edematous arytenoid, or submucosal swelling in the posterior pharyngeal wall should raise suspicion of a malignant lesion. Cancers confined to the postcricoid area often evade detection in office laryngoscopy but can be suspected in the presence of edematous arytenoids and/or fixed hemilarynx. Anterior traction on the larynx by grasping the overlying skin and pulling forward may improve the view.

The examination of the neck should include careful palpation on both sides and assessment for number, level, size, and mobility of any enlarged lymph nodes. Tenderness over the lateral expansion of the laryngeal framework or upper trachea may suggest cancer invasion. A side-to-side movement of the laryngeal framework is recommended to assess the laryngeal crepitus at the level of thyroid cartilage. Fixation of cancer to the prevertebral fascia or anterior displacement of the larynx by advanced postcricoid and posterior wall tumors can result in loss or restriction of laryngeal crepitus.

Imaging

Radiologic studies such as contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) are performed to complete the diagnostic

evaluation. Compared to CT, MRI is more susceptible to motion artifacts from swallowing, coughing, or any other movement and is usually the second line of investigation; it may however be preferred to assess cancers that recur after resection or chemoradiation for better tissue delineation.[3] Radiology complements physical examination with information about the inferior extent of cancer, submucosal spread, invasion of the thyroid cartilage, and extralaryngeal involvement. Involvement of the prevertebral fascia or space should be ruled out for the primary cancers arising from or extending to the posterior wall of the pharynx. Imaging can also reveal the presence of a synchronous primary cancer, which is known to have a high incidence in the hypopharynx and cervical esophagus due to *field cancerization* effects from chemical carcinogens. Barium swallow is helpful in ruling out an esophageal cancer. It also facilitates diagnosis of esophageal motility disorders in patients with progressive dysphagia with no risk factors for SCC and a normal physical examination. Endoscopic ultrasonography is considered to be a more accurate imaging technique in determining the T stage of cancers of the cervical esophagus.

Ultrasonography and CT are of help in an accurate search for lymph node metastases; the latter is superior in demonstrating RPLN metastases. High rates of distant metastases of 10% to 30%[1,14,15]are associated with cancers of the hypopharynx and cervical esophagus. Hence, screening with whole-body positron emission tomography (PET) or chest and abdominal CT scans is recommended, particularly in patients with prolonged symptoms and bulky lymph node metastases.

Endoscopy Under Anesthesia and Biopsy

Examination under anesthesia (EUA) of the pharynx, larynx, trachea, and esophagus under anesthesia with rigid endoscopes is fundamental to accurately evaluate the cancer site and stage and detect synchronous primary cancer of the UADT. A rigid esophagoscopy is required to assess spread of the cancer to the cervical esophagus and to rule out a synchronous esophageal primary cancer. EUA allows tissue biopsy for diagnostic confirmation, although a histologic diagnosis can be achieved with fine-needle aspiration in patients with palpable neck nodes. In patients with advanced cancers and widely scattered foci of dysplastic-appearing mucosa in the UADT, mapping biopsies are a useful aid to predict resectability. Mapping biopsies are also

important for chemoradiation-recurrent cancers; many of these cancers do not exhibit typical clinical or radiologic findings, and malignant tissues may lurk beneath intact mucosa far distant from the epicenter of the primary cancer. Palpation of the cancer and movement of the cancer over the prevertebral fascia help to ascertain fixation for cancer of the posterior wall of the hypopharynx. Bronchoscopy is recommended for patients with cancer of the cervical esophagus in order to detect anterior extension of the cancer or a synchronous primary cancer. Based on information from clinical, radiologic, and endoscopic evaluations, a final clinical tumor stage (cT) is determined (**Table 16.1**) according to the American Joint Commission Cancer (AJCC) staging system. EUA for cancer of the hypopharynx also gives an opportunity to determine the access and feasibility for resection via a transoral approach. In cases unsuitable for transoral resection, assessment is directed toward decision-making for conservation versus radical surgical approaches and/or nonsurgical management. Assessment of the extent of the anticipated pharyngeal defect from surgical resection, as well as the most appropriate type of reconstruction, should be made during EUA. For patients likely to undergo a flap reconstruction, a donor site and potential alternatives should be planned.

Table 16.1 American Joint Committee on Cancer T and N Staging of Hypopharynx and Cervical Esophagus Cancer (2010)

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Hypopharynx	
T1	Tumor limited to one subsite of the hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of the hypopharynx or an adjacent site or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of the hemilarynx
T3	Tumor more than 4 cm in greatest dimension or with fixation of the hemilarynx or extension to the esophagus
T4a	Tumor invades the thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue, which includes prelaryngeal strap muscles and subcutaneous fat
T4b	Tumor invades the prevertebral fascia, encases the carotid artery, or involves mediastinal structures
N staging	
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Esophagus	
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading the pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, trachea, etc
N staging	
N1	Metastasis in one to two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes

Additional Investigations

Routine hematologic and blood chemistry investigations are performed as part of pretreatment evaluation. Assessment of iron deficiency is particularly relevant in females with features of Plummer-Vinson syndrome. Protein deficiency and overall nutritional status should also be evaluated, and corrective measures initiated prior to initiation of treatment. The cachectic patient may benefit from pretreatment insertion of a percutaneous endoscopic gastrostomy (PEG) tube. A majority of patients are heavy smokers; hence, pulmonary reserve is checked with careful history and pulmonary function

tests, and referrals to tobacco cessation programs are made. Patients with poor pulmonary reserve may not be candidates for transoral or open conservation surgery due to the high risk of developing pulmonary complications from postoperative aspiration. Assessment of dentition is done during office examination, and referral is made to a specialist if restorative procedures or dental extractions are required, particularly for patients who are planned to receive radiation as part of the treatment.

Treatment

Among all cancers of the UADT, SCC of the hypopharynx and cervical esophagus are known to have an unfavorable prognosis. Treatment is aimed at achieving locoregional control with improved survival and a good functional outcome. Resectability of the primary cancer and nodal metastasis, medical comorbidities, pulmonary function status, patient preference, and distant metastasis at presentation are the important considerations in making treatment decisions. Surgery followed by adjuvant treatment for adverse features is the most commonly used approach for treatment of cancer of the hypopharynx.[5] Single modality therapy with surgery or radiation alone may be an effective therapeutic approach for early T1 or T2 disease, but most of these cancers are diagnosed at a more advanced stage. For advanced cancer, the most common conventional treatment approach has been partial or total pharyngectomy with a total laryngectomy. With a goal to cure and to preserve the larynx, nonsurgical treatment approach with various chemoradiation protocols started to gain favor in the late 1990s.[1,16] The risk of long-term toxicity, principally dysphagia and aspiration, from chemoradiation and poor outcomes after salvage surgery for postchemoradiation-recurrent tumors[16–18] rekindled interest in organ-preserving, conservative surgical approaches including transoral laser microsurgery (TLM).

For SCC of the cervical esophagus, radical surgery with laryngopharyngoesophagectomy and adjuvant radiotherapy was regarded as the gold standard of treatment. Nonsurgical approaches have been employed as alternatives to radical resection; newer, minimally invasive thoracoscopic surgery is also evolving for early cancers of this site.

Surgical Treatment

The goal of surgery is to achieve a resection with clear margins with or without laryngeal preservation, and extent of surgery is dictated by the site of the cancer, its stage, and functional status at presentation as well as the patient’s pulmonary reserve. Extension of cancer to the vertebral column and mediastinal structures and encasement of the carotid artery(s) are often features associated with unresectable cancer. When feasible, conservation surgery is performed with the objective to cure, minimize operative morbidity, and maximize function and quality of life (QOL). Laryngeal preservation with a transoral approach facilitates faster recovery of swallowing compared to conventional, open conservation approaches, due to better preservation of suprahyoid musculature, constrictor muscle, and the pharyngeal neural plexus.

Transoral Approaches

Transoral Laser Microsurgery

TLM as an approach for the management of hypopharyngeal SCC was first reported by Steiner in 2001.[19] When feasible, this approach reduces the need for permanent tracheotomies or feeding tube dependency by avoiding resection of tissues that are critical for airway, speech, and swallowing functions. The application of TLM to resect select advanced SCC of the hypopharynx has broadened as experience and technology advance.

Contraindications: Inadequate access is the most important contraindication for TLM resection of cancer of the hypopharynx. Extensive invasion of the larynx and base of the tongue and bilateral arytenoid extension or fixation preclude function-preserving conservation surgery, and thus, patients with these features will not benefit from transoral resection. Circumferential or near-circumferential spread to the cervical esophagus, gross invasion of the cricoid cartilage, significant extralaryngeal spread, and encroachment on major vessels in the neck are other contraindications for TLM in cancer of the hypopharynx. Patients with cancer of the posterior pharyngeal wall with invasion into the prevertebral and parapharyngeal spaces are also not suitable for TLM.

Technique: Resection in TLM is performed using the principles first popularized by Steiner.[20] Access is achieved with a combination of distending or fixed bore laryngoscopes (e.g., Steiner, Kleinsasser, Lindholm) or bivalved scopes. A key maneuver to enhance exposure of the tumor and surrounding landmarks, especially in patients with redundant, collapsing mucosa, is to maximally suspend and distend the long Steiner endoscope, thus creating luminal working space. For exophytic cancers, debulking at the onset also creates improved exposure of the surgical field. The CO_2 laser beam is usually delivered to the operative site via a micromanipulator attached to the operating microscope. TLM is initiated with a *transtumoral* incision, which transects the cancer for depth estimation, and is completed by *multibloc* resection until negative margins are obtained (**Fig. 16.2**). Mucosal margins of at least 5mm for superficial and 10mm for infiltrating cancers are recommended; however, confirmation of margin-negative resection by frozen sections from the perimeter of the resection defect is fundamental to the TLM technique. The principles of TLM resection of SCC of the hypopharynx are outlined in **Table 16.2**, and hypopharyngeal subsite-specific resection techniques are discussed below.

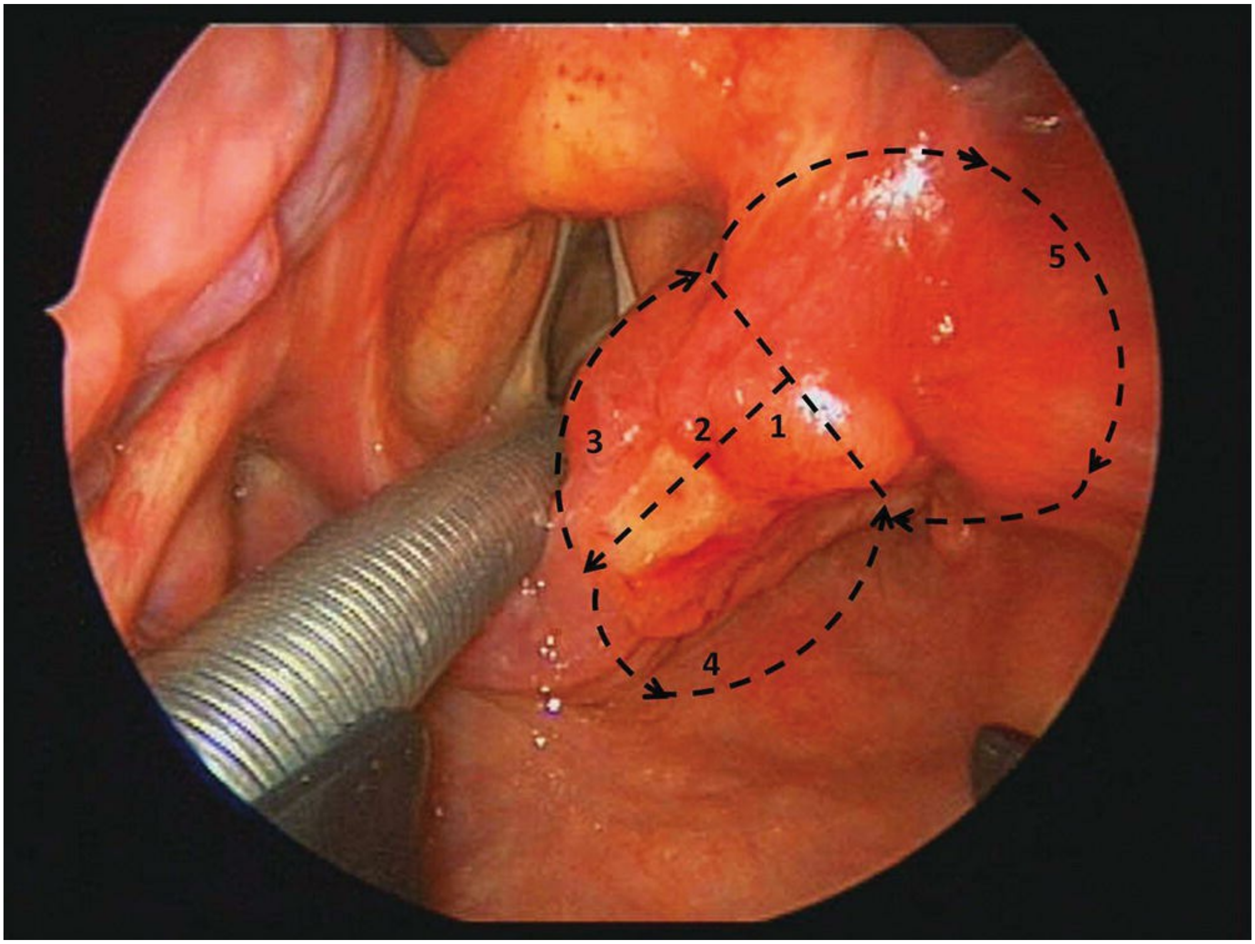


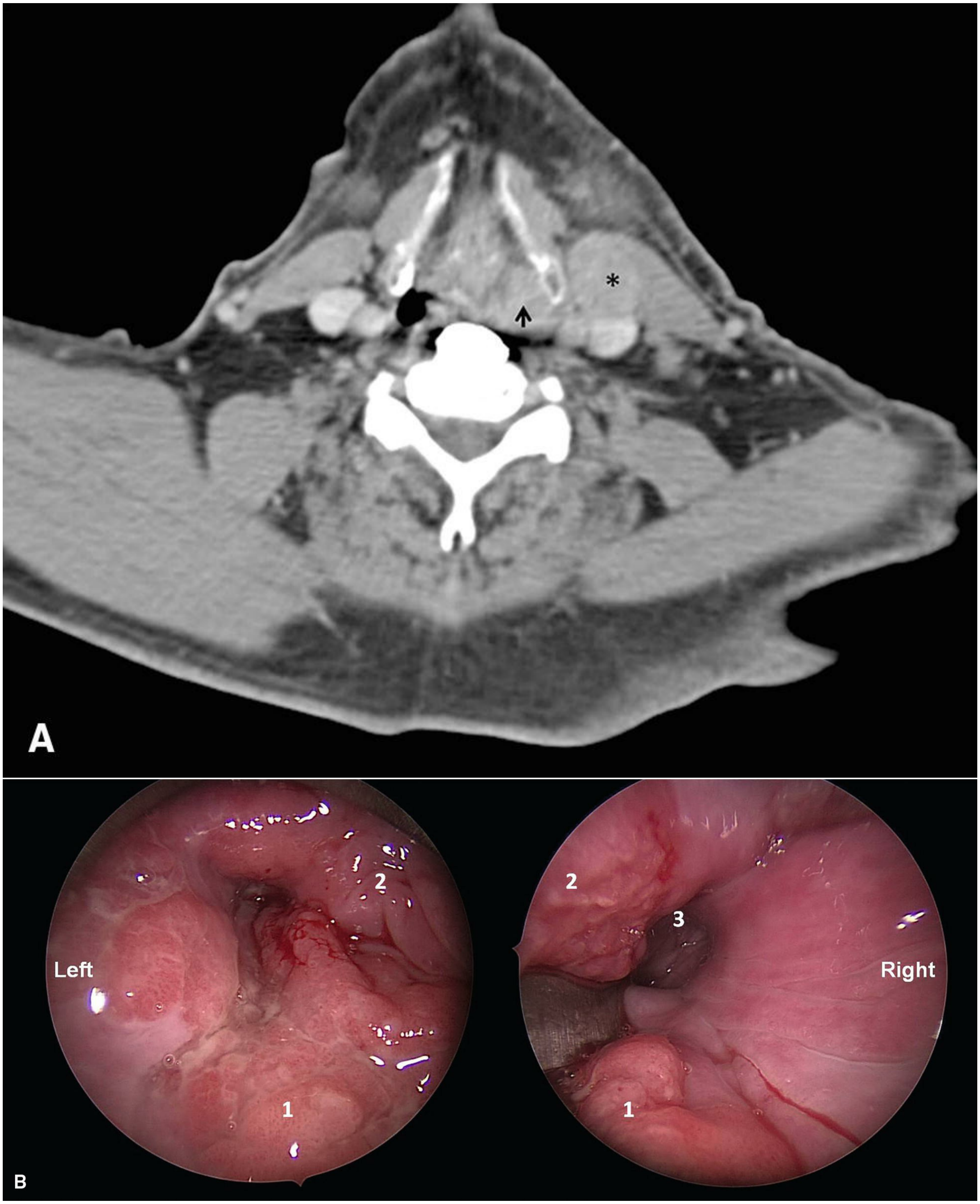
Figure 16.2. Sequential incisions and *multibloc* design for TLM resection of the medial wall of the right pyriform sinus/aryepiglottic fold (AEF) cancer ([*1*] transverse *transtumoral* cut, [*2*] longitudinal, splitting posterior AEF cut, [*3* and *4*] completion medial [*3*] and lateral [*4*] AEF/arytenoidectomy cuts at perimeter, [*5*] anterior AEF, lateral epiglottic and PFS wall cut).

Table 16.2 Requisites and Fundamental Principles of Hypopharynx SCC Management with TLM Approach

Preoperative	
▪	Knowledge of "inside-out" anatomy for transoral resection and patterns of tumor spread
▪	Training in the instrumentation and techniques of TLM
▪	Rigid endoscopic examination under anesthesia to evaluate access and feasibility of complete transoral oncologic resection
Operative	
▪	Maximal endoscope distension and suspension, for luminal expansion
▪	Debulking for exophytic tumors to create access
▪	Transtumoral cuts for depth assessment
▪	*Multibloc* tumor resection in craniocaudal direction
▪	Meticulous hemostasis: vessel control with clips during TLM resection and prophylactic ligation during neck dissection
▪	Combined approach via lateral pharyngotomy if indicated by limited access or tumor extent
▪	Neck dissection in the same operative session
▪	Prophylactic tracheotomy in patients with poor performance status or body habitus or resection that includes the arytenoid or paraglottic space or deep mucosal space
Postoperative	
▪	Swallowing and speech rehabilitation with a speech pathologist
▪	Pathologic risk factor-based adjuvant therapy

Pyriform sinus: Resection commences proximally and advances distally in a craniocaudal direction,[20] widening the exposure as incisions are made around the anterior extent from the lateral toward the medial side (**Fig. 16.3**). Another approach is first to divide and resect the AEF and then proceed on to

removal of the anterior and lateral components. Extension into the pre-epiglottic space is also addressed early in a TLM approach, thereby facilitating exposure. For cancers involving the medial PFS that approach, but do not frankly invade, the AEF and the arytenoid cartilage, complete oncologic clearance can be achieved by carefully peeling the mucosa from the surface of the arytenoid without sacrificing the cartilage itself. This technique minimizes the risk of aspiration versus a more extensive arytenoidectomy to facilitate postoperative swallowing. In patients for whom the arytenoid needs to be resected, preservation of at least one functional arytenoid is required to prevent aspiration. For cancers of the lateral PFS that approach the thyrohyoid membrane, the membrane may be excised as a margin and the tumor is followed out to the strap muscles, if required. Thyroid perichondrium may also be stripped off to ensure clear margins, but delayed healing may result. For cancers that infiltrate the thyroid cartilage, the involved areas of the cartilage are resected along with accessible extracartilaginous extensions. For extensions of the cancer that are not completely accessible, the transoral approach can be combined with a lateral pharyngotomy parallel to and posterior to the thyroid lamina, using the access provided by the neck dissection. This approach is also used in situations where there is inadequate access to resect extensions of the cancer of the PFS. The pharyngotomy or laryngotomy is repaired by advancement of the constrictor muscles and adjacent strap muscle and/or an additional patch of cadaveric acellular dermis.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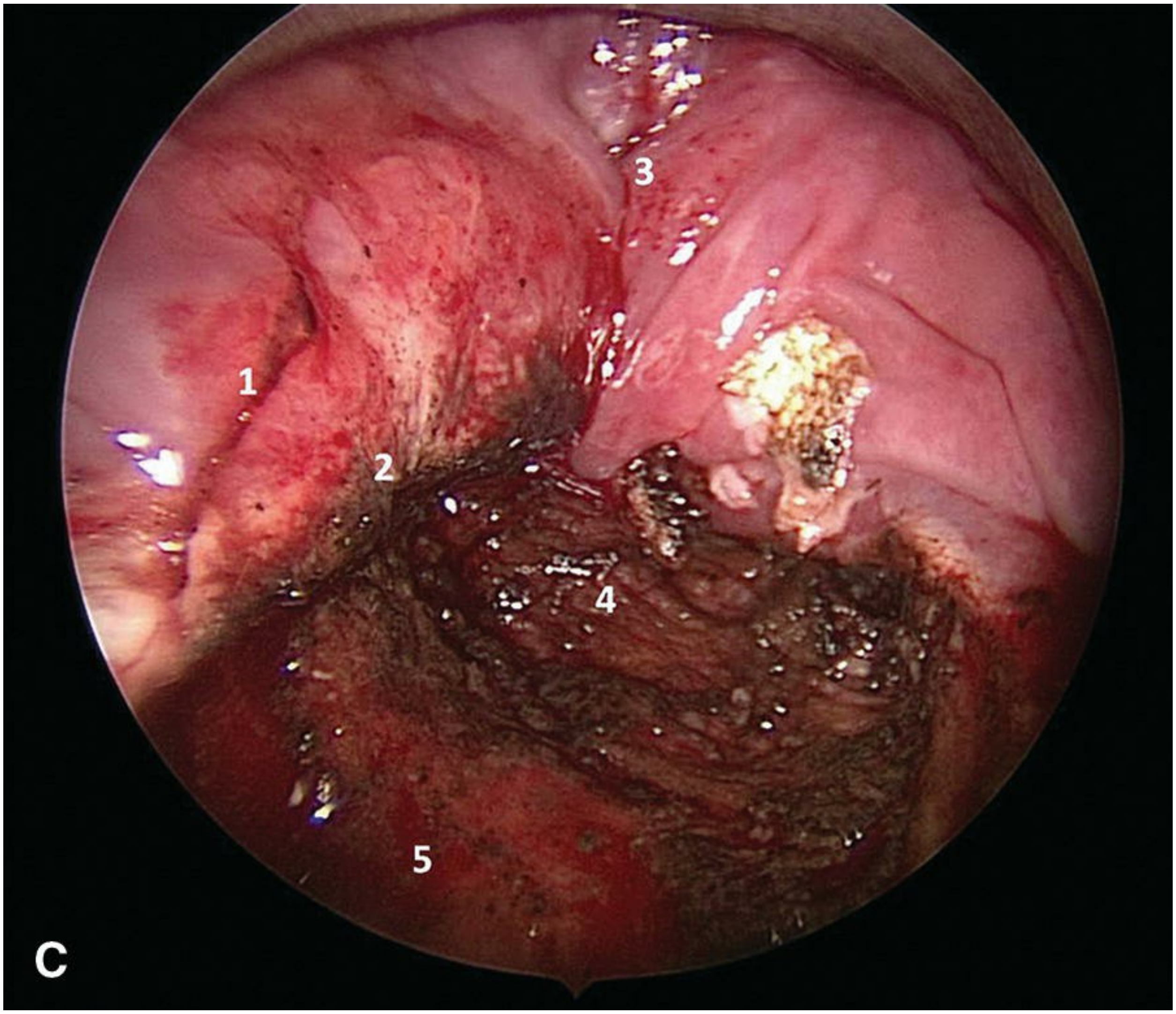
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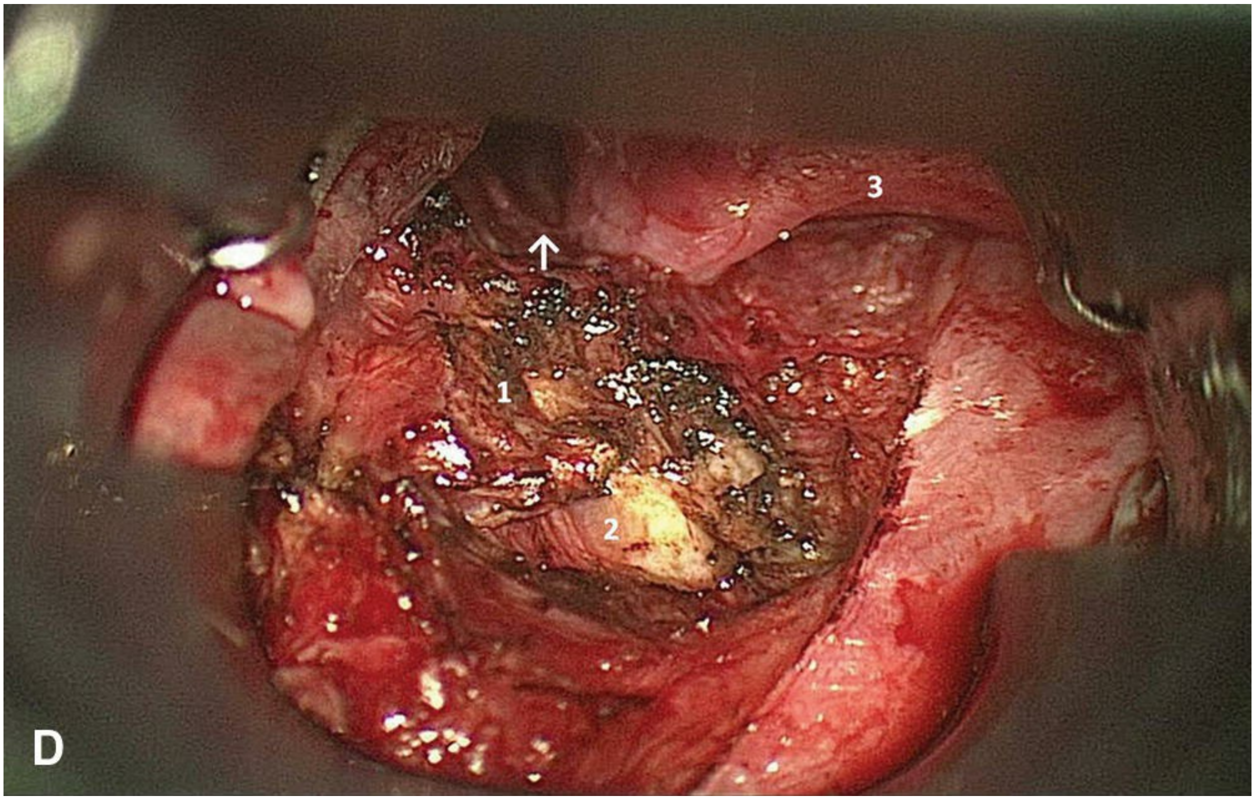


Figure 16.3. TLM resection of T3 pyriform SCC. **A:** Axial CT image demonstrating cancer in the left PFS (*arrow*) with an adjacent level III metastatic lymph node (*asterisk*). There is no evidence of thyroid cartilage invasion. **B:** Preoperative endoscopic images of the cancer of the left PFS with extension of the cancer into the anterior and medial walls of the PFS and the posterior wall of the hypopharynx; the contralateral right PFS is uninvolved. Note extension to the left post cricoid area, with a clear esophageal inlet ([*1*] posterior wall of the hypopharynx, [*2*] postcricoid area, [*3*] esophageal inlet). **C:** Intraoperative image showing resection bed ([*1*] lateral wall of the PFS, [*2*] thin layer of soft tissue overlying the left thyroid cartilage, [*3*] anterior remnant of the cancer awaiting resection, [*4*] left posterior cricoarytenoid muscle, [*5*] posterolateral wall of the left hypopharynx). Resection included the medial walls of the PFS, anterior wall of the PFS, the pharyngoepiglottic fold, the pre-epiglottic space, and a component of the lateral pharyngeal wall. **D:** Postoperative image of the superior, oropharyngeal extent of the resection bed ([*1*] constrictor muscles, [*2*] prevertebral fascia, [*3*] epiglottis). *Arrow* denotes the point from which the resection continued into the left PFS.

Postcricoid area: TLM can be used for cancers that are superficial and

confined to the postcricoid area. For cancers with minimal inferior extension into the esophageal inlet, a long expanding or bivalved laryngoscope is used to gain access. Excision is performed down the upper esophagus in separate blocs by making longitudinal, then curvilinear incisions around the inlet and assessing the specimen for complete clearance of the cancer with a margin of normal esophageal mucosa. No more than 180 degrees of the circumference should be demucosalized. Because the operative field is very close to the posterior cricoarytenoid muscle, resection should be extremely cautious because there is a high risk of postoperative airway compromise due to injury to the sole abductor muscle of the vocal cord.

Posterior wall of the hypopharynx: Cancers in this subsite usually have excellent transoral access (**Fig. 16.4**). TLM incisions can be used to detect and follow cancer infiltration into or beyond the buccopharyngeal fascia, even into the prevertebral fascia. Even though there is limited or focal infiltration of the prevertebral fascia, the musculature and the anterior spinal ligament can be adequately addressed by TLM, although there is a risk of postoperative complications such as vertebral osteomyelitis or abscess, especially after adjuvant radiotherapy.

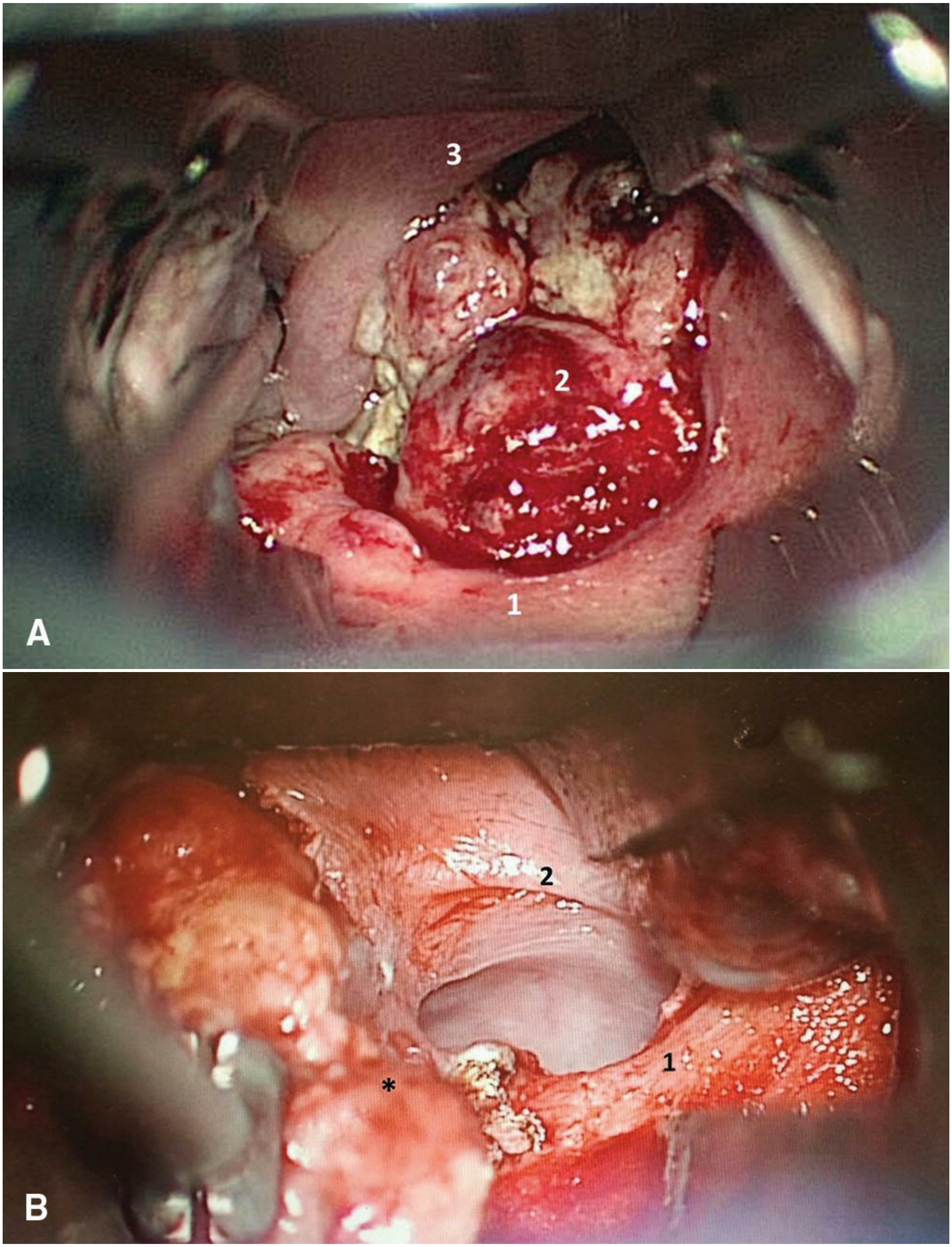


Figure 16.4. TLM resection of an exophytic cancer of the posterior wall of

the hypopharynx, abutting but not invading the postcricoid area and extending inferiorly to the esophageal inlet. **A:** Preoperative endoscopic image of the cancer ([*1*] posterior pharyngeal wall, [*2*] cancer, [*3*] postcricoid area). **B:** Intraoperative image depicting the esophageal inlet prior to resection of the final segment (*8 o'clock). Note intact mucosa at anterior and right lateral 180 degrees ([*1*] resection bed, [*2*] intact mucosa with cervical esophageal lumen distally).

Postoperative care: Patients with TLM resection for early-stage cancer tolerate extubation well or may require an overnight intubation. Tracheostomy for protection from aspiration is performed in patients with advanced cancers who undergo significant resection, particularly when the arytenoid or paraglottic space is involved. Three weeks of prophylactic, broad-spectrum antibiotics and antireflux agents is initiated. A nasogastric tube is inserted to maintain nutrition in the immediate postoperative period, which may be replaced by a PEG for patients with resection of advanced cancers.

Complications: A complication rate of 4% to 19% has been reported across several studies; the majority and most serious of these complications are postoperative bleeding, aspiration, and laryngeal edema. A few of these complications have been described as life threatening in certain studies, but none of the events have led to a perioperative death in the authors' experience. The complication rates have been significantly associated with the surgeon's experience and extension of the primary cancer.[16] Patients with deep mucosal resection are at increased risk of postoperative hemorrhage so that a tracheostomy is recommended at the end of the procedure to protect the airway. Also, critical in minimizing the risk of bleeding is observance of meticulous hemostasis with clipping and cautery of exposed superior and inferior laryngeal arteries or their branches during TLM.[21] It is also helpful to ligate and divide named vessels during the neck dissection that have been transected at the primary site. Infection and pharyngocutaneous fistula are rare complications of TLM when compared to open surgical approaches.

Endoscopic access can cause pressure-related complications such as dental trauma, tears of the wall of the pharynx, edema of the tongue, and injury to the lingual, glossopharyngeal, or hypoglossal nerves.[22] Laser-related burns or airway fires are particularly rare but are preventable risks with

adequate safety precautions, such as a laser-proof endotracheal tube and an oxygen-depleted anesthetic environment.

Transoral Robotic Surgery

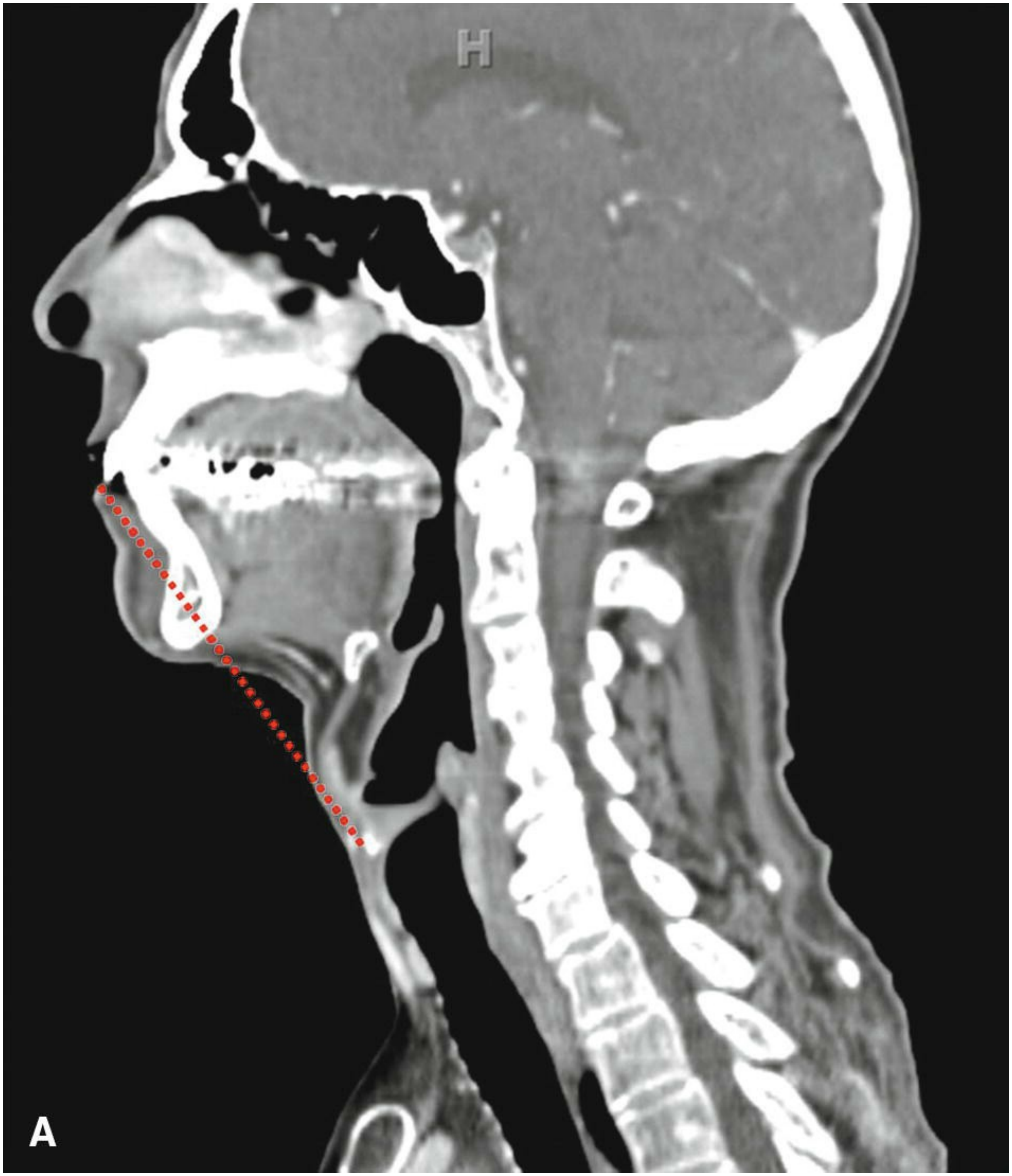
Transoral robotic surgery (TORS) with the da Vinci Surgical System-assisted hypopharyngectomy is an evolving approach, the application of which was first reported in 2010 for resection of early-stage SCC of the PFS and posterior pharyngeal wall.[23]

Technique: The Feyh-Kastenbauer retractor is used to obtain an optimal view of the working space. An 8-mm 30-degree endoscopic camera is inserted into the oral cavity. The two robotic arms on either side of the camera are equipped with 5-mm-sized instruments; one of which is used for tissue retraction or dissection, whereas the other arm carries the unipolar cautery for making incisions. Cancers are resected en bloc. Cancers of the PFS are resected in the shape of a cone with the first incision being made in an anterior to posterior direction along the medial side of the AEF, preserving the arytenoid. This is followed by medial to lateral dissection along the thyroid cartilage where the perichondrium is incised horizontally and the inner perichondrium of the thyroid cartilage is peeled off. The dissection continues along the lateral side of the thyroid cartilage followed by dissection in the posterior part where a portion of the inferior constrictor muscle in the posterior pharyngeal wall is included as a posterior margin.

Postoperative care and complications: Postoperative care is similar to post-TLM resection. The largest published series on outcomes of 23 patients with cancer of the hypopharynx treated with TORS, from Korea, reported postoperative bleeding as the only complication.[24]

TLM versus TORS: A multiangled view of the surgical field, greater mobility of EndoWrist instruments and absence of “line-of-sight” limitation of the microscopic view are cited as advantages of TORS over TLM. However, compared to TLM, TORS can be applied to only select, early cancers of the hypopharynx. Submucosal spread is a common feature of cancers of the hypopharynx, and compared to en bloc resection in TORS, TLM better facilitates oncologic clearance by sequentially following the submucosal extensions while preserving normal structures. Access through the FK retractor may not give exposure of certain anterior and inferior

locations for complete resection of the cancers. These locations can be accessed only by appropriate positioning maneuvers via laryngoscopes (**Fig. 16.5**) through which passage of the currently available TORS instrumentation, let alone creation of working space, is infeasible. Moreover, monopolar cautery, the cutting tool in TORS, causes greater thermal damage and risks electrical damage to the recurrent laryngeal nerve. Cutting with the CO_2 laser fiber has the benefits of precision but with minimal blood loss as it seals vessels smaller than 1mm. Improvement in instrumentation, with added flexibility and miniaturization, may increase the applicability of TORS for resection of cancer of the hypopharynx.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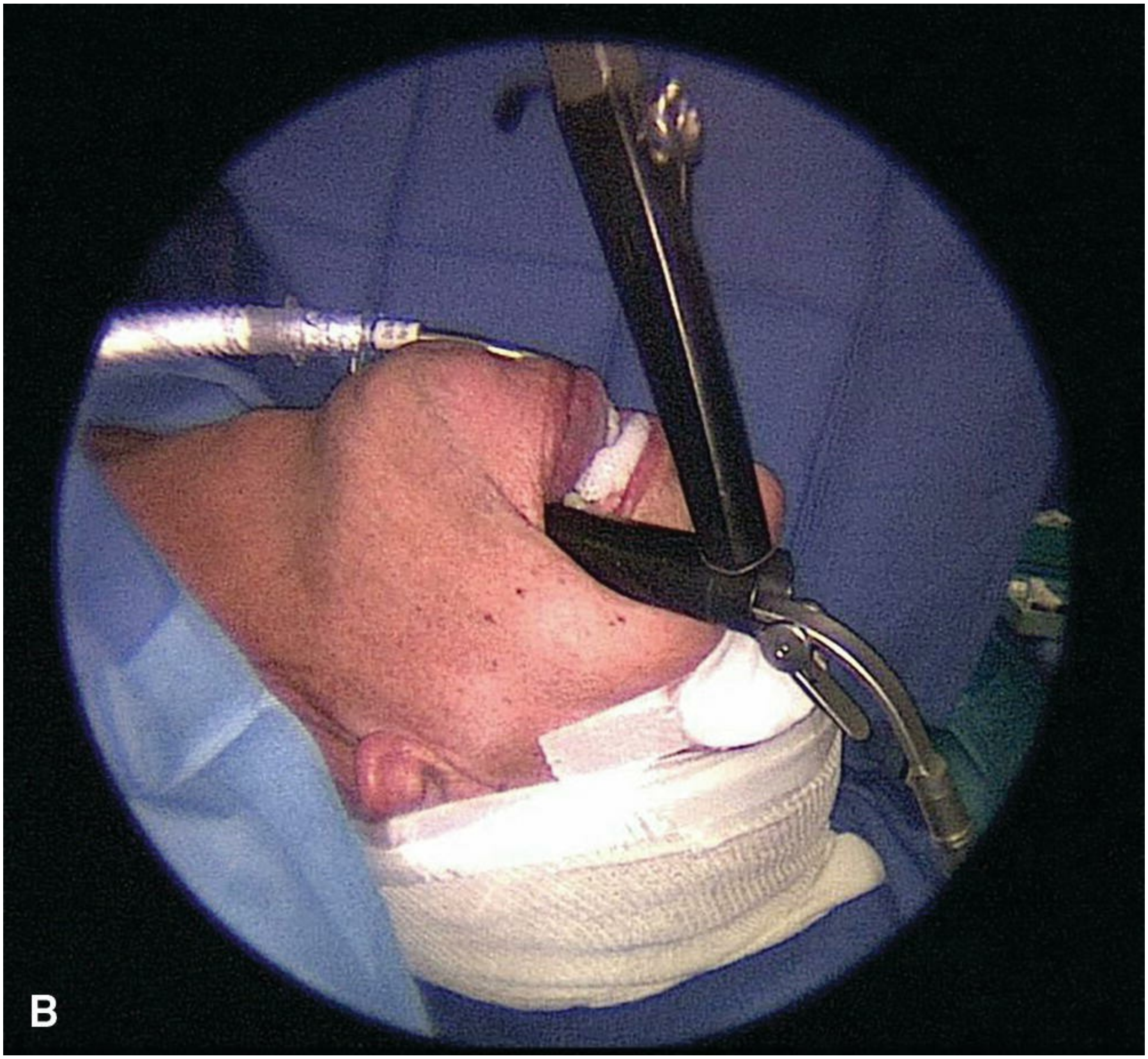
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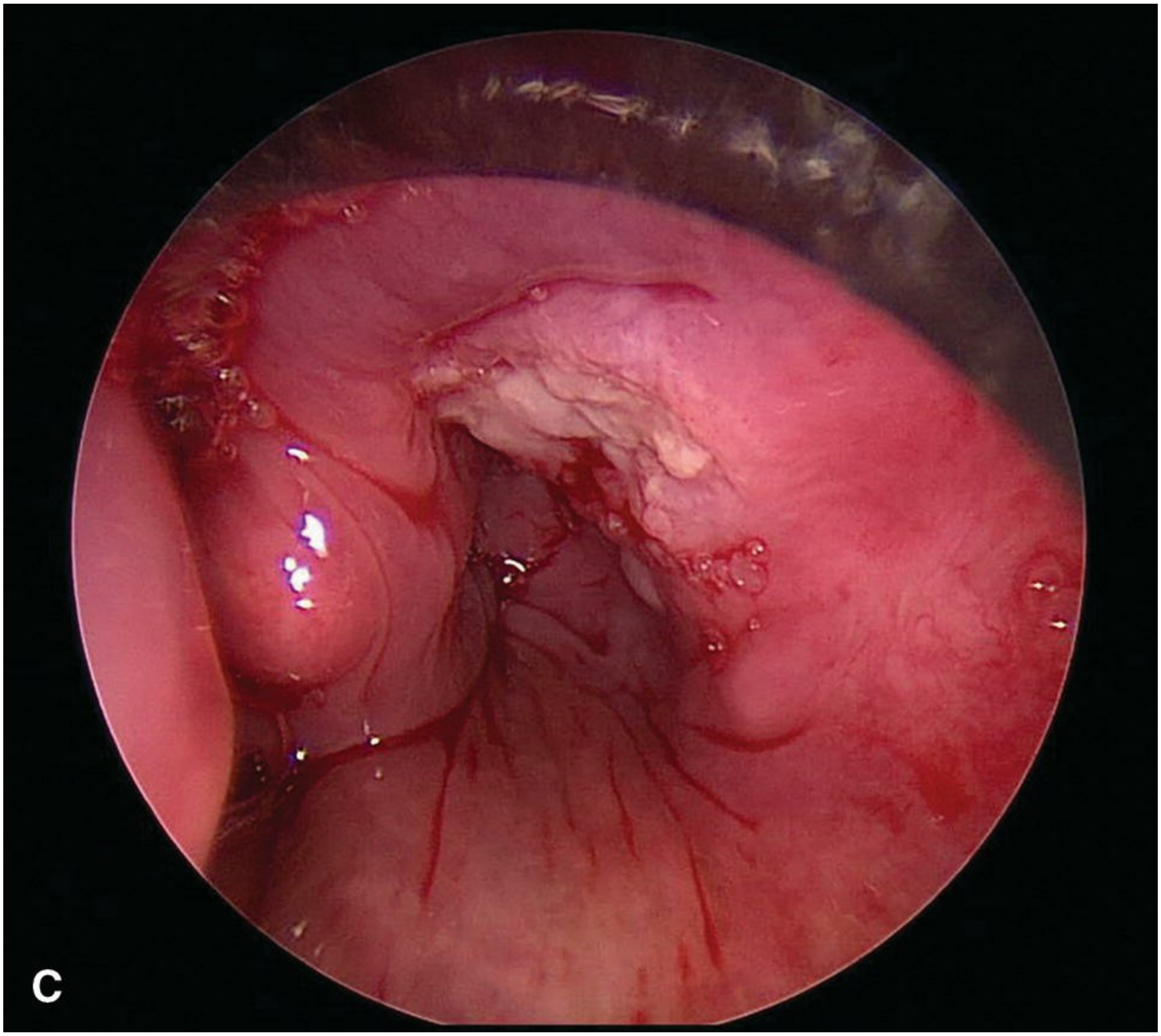
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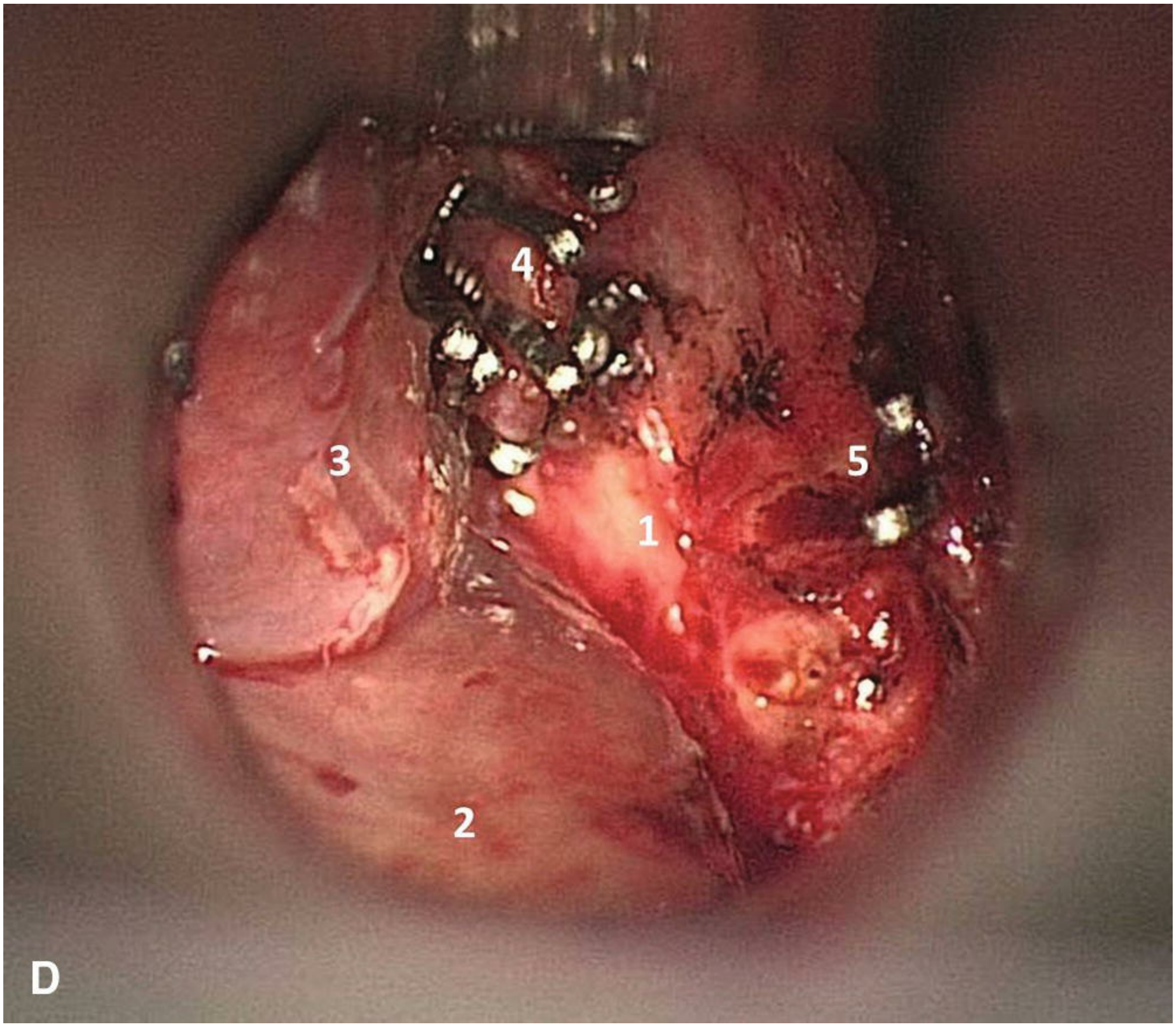


Figure 16.5. TLM resection of T2 right PFS cancer in a patient with difficult access. **A:** Sagittal image on CT showing the hyomandibular relationships, dotted line depicts improbability at *midline* of rigid endoscopic access. Note cervical osteoarthritis, which further limits neck extension. **B:** Endoscopic setup using fixed bore Steiner glottiscope. Note the angulation of the glottiscope from the patient's proximal left to distal right that circumvents the central incisors and unfavorable hyomandibular relationship as seen in image A. **C:** Endoscopic preoperative image showing good exposure of the cancer in the right lateral PFS. **D:** Postresection image ([*1*] right PFS resection bed, [*2*] right intact posterior wall of the hypopharynx, [*3*] right arytenoid, [*4*] clipped right inferior laryngeal artery, [*5*] clipped right superior laryngeal artery).

Open Approaches

Conservation Surgery

Open conservation procedures with partial resection of the pharynx and laryngeal preservation for select cancers of the hypopharynx have now been mostly supplanted by transoral approaches, provided the criteria of access are met as described above. The traditional open conservation procedures performed through incisions in the neck are discussed below. A temporary tracheostomy is usually performed at the onset or after these procedures to avert airway complications, which may occur from postoperative mucosal edema.

Partial Pharyngectomy

Partial pharyngectomy for cancer of the hypopharynx through a lateral pharyngotomy approach was first described by Trotter. It can be used safely to extirpate early cancers of the superior aspect of the PFS or the posterolateral wall of the hypopharynx.[25–27] It can also be used in combination with the TLM approach for resection of primary cancers of the hypopharynx that cannot be excised completely transorally due to difficult access or difficulty in approaching the inferior or lateral extensions of the cancer. This approach is contraindicated in the presence of extension below the level of the arytenoids, extension to the postcricoid area, or fixation of cancer to the posterior wall. The exposure to perform the pharyngotomy is usually available through the incision for neck dissection, which is required in most of the patients with hypopharyngeal cancer in order to surgically address the regional lymph nodes. The inferior constrictors are divided at the posterolateral border of the thyroid cartilage, and the posterior surface of the superior aspect of the thyroid cartilage is separated from the pharyngeal mucosa to perform a “pyriformotomy” for approaching the primary cancer. Occasionally, the posterior border of the thyroid cartilage may need to be sacrificed for obtaining complete access. Caution is exercised to preserve the superior laryngeal nerve for better functional outcomes.

A transhyoid approach through the body of the hyoid has been described to perform a pharyngotomy for excision of cancer of the posterior hypopharyngeal wall, but the exposure is limited for achieving complete oncologic resection.

The pharyngotomy defect is usually amenable to primary closure: reinforced by local rotation flaps or acellular dermal graft. Small, <1 cm posterior pharyngeal wall defects can heal by secondary intention; larger defects may require a split thickness graft and, rarely, a pedicled or microvascular free flap.[25] Defects extending to the lateral wall of the hypopharynx may require a local muscle rotation flap.

Partial Pharyngectomy with Supraglottic Laryngectomy

This procedure, described in the early 1960s by Ogura et al.,[28] can be used for resection of cancers in the medial or anterior wall of the PFS or in the posterior wall of the hypopharynx. Poor pulmonary status, restricted mobility of the vocal cord or arytenoid, extension to the base of the tongue, involvement of the apex of PFS or the postcricoid area, and invasion of the thyroid cartilage are contraindications for this procedure. The hypopharynx is entered through the vallecula away from the side of the cancer, and the cancer is resected under direct view while maximally preserving the pharyngeal wall. The ipsilateral supraglottic larynx is included in the resection; the vocal cords are preserved bilaterally.

Closure is achieved by approximating the base of the tongue to the larynx with sutures between the tongue musculature and the thyroid perichondrial flap. It is reinforced by suturing the cut ends of strap muscles without creating any tension on the pharyngeal repair. Reconstruction with a free fasciocutaneous flap may achieve better function for larger pharyngeal defects.

Partial Pharyngectomy with Supracricoid Laryngectomy or Supracricoid Hemilaryngopharyngectomy

Supracricoid laryngectomy or supracricoid hemilaryngopharyngectomy (SCHLP) was first reported in the mid-1960s and later popularized by Laccourreye for treating selected cancers of the PFS with laryngeal preservation. It involves resection of the ipsilateral PFS from the level of the vallecula to the apex, the ipsilateral hemilarynx above the superior border of the cricoid cartilage, and the epiglottis and pre-epiglottic space as required.[29]

This technique provides a better access to resect the cancers of the medial and lateral walls of the PFS and can be performed in the presence of thyroid cartilage invasion or arytenoid fixation, both of which are contraindications for the procedure of partial pharyngectomy with supraglottic laryngectomy. SCHLP is contraindicated in the presence of a fixed hemilarynx, paraglottic space extension, postcricoid and PFS apex involvement, cricoid cartilage invasion, and extralaryngeal spread.

Pharyngeal and laryngeal closure up to the level of the contralateral false cord is achieved with a flap innervated by the contralateral superior laryngeal nerve and comprised of the mucosa of the contralateral posterior pharyngeal wall. The inferior defect is repaired with the musculoperichondrial flap comprised of infrahyoid muscles and thyroid external perichondrium preserved during laryngeal exposure.[29] Postoperatively, these patients may require a tracheostomy and a feeding tube for a longer period compared to patients undergoing a transoral approach.

Radical Surgery

Near-Total Laryngectomy with Partial Pharyngectomy

The technique of near-total laryngectomy was first described by Pearson in 1981.[30] It can be performed for locally advanced cancer of the PFS in the presence of a fixed hemilarynx. The presence of a contralateral, mobile arytenoid, sufficient contralateral disease-free pharyngeal mucosa for the fashioning of a voice shunt, and uninvolved interarytenoid and postcricoid regions are essential for the procedure. The resection specimen consists of the PFS, the hemilarynx including upper tracheal rings, and the thyroid lobe on the ipsilateral side along with the entire epiglottis and the pre-epiglottic space. The contralateral arytenoid and the posterior portions of false and true vocal cords are preserved along with the cricoarytenoid joint and the recurrent laryngeal nerve. Pharyngeal repair with or without regional or free flaps and creation of a tracheopharyngeal shunt facilitate speech and swallowing; the airway is maintained with a permanent tracheostomy.

Total Laryngectomy with Partial Pharyngectomy

Patients with advanced postcricoid cancer and cancer of the PFS with extension to the apex or cricoid cartilage, bilateral arytenoid invasion,

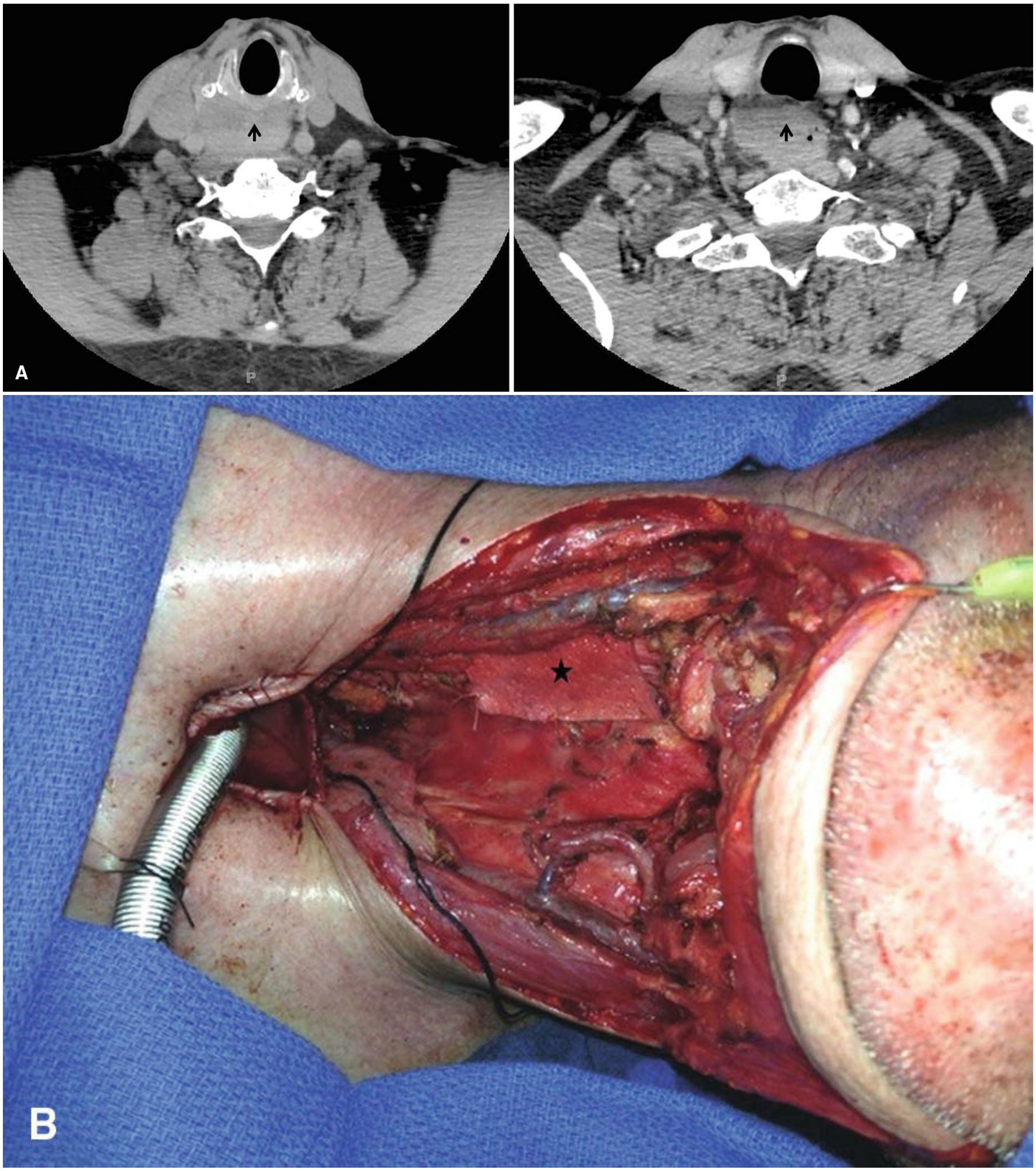
extensive thyroid cartilage, or extralaryngeal invasion are not candidates for laryngeal preservation surgery. Surgery for such cancers requires a total laryngectomy with partial or total pharyngectomy and often a hemithyroidectomy. A tight pharyngeal closure increases the risk of fistula formation and postoperative dysphagia. Hence, primary closure should be performed only if the remnant pharyngeal mucosa is sufficient to close around a 36-French dilator; such defects ideally are less than one-third of the circumference.[31] Larger pharyngeal defects require a “patch” reconstruction with a pedicled myocutaneous or a free fasciocutaneous flap such as radial forearm or anterolateral thigh flap.

Total Laryngopharyngectomy

Total resection of the pharynx with a total laryngectomy is required for SCC of the hypopharynx that are too advanced to be resected with sufficient uninvolved mucosa. Surgery for postcricoid cancers, PFS cancers with extension to the postcricoid area, and cancer of the posterior hypopharyngeal wall with extension below the arytenoids results in circumferential defects, which require a tubed reconstruction of the pharyngeal segment. Resection may also involve portions of the upper esophagus to achieve negative margins. In brief, bilateral sharp skeletonization and blunt skeletonization of the lateral larynx and pharyngeal wall, followed by opening, blunt dissection of the prevertebral space, a suprahyoid pharyngotomy, and transection of the pharynx, and tracheal and esophageal transection inferiorly are the standard surgical steps. A variety of techniques have been described for reconstruction, some of which are only of historic note. Nowadays, the most commonly used techniques are reconstruction with a tubed pedicled flap or a microvascular free flap, the latter being the option of choice. A pedicled regional flap such as a pectoralis major myocutaneous or, less commonly, a deltopectoral fasciocutaneous flap is used in patients unfit for microvascular reconstruction.

A tubed radial forearm free flap (RFFF) provides excellent functional reconstruction with minimal donor site problems and may be modified to incorporate reconstruction with the neck skin (**Fig. 16.6**).[32] In forearm donor sites unfit for RFFF harvest and in patients with a suitable body habitus, the anterolateral thigh flap may be used (**Fig. 16.7**).[33] Free jejunal grafts have been used as one of the reconstructive options because the caliber of the

jejunum closely matches that of the upper esophagus. However, abdominal donor site morbidity, suboptimal quality of swallowing, and tracheojejunal voice[34] do not make it a preferred reconstruction option. Other reported reconstructive options with free tissue transfer include lateral thigh, latissimus dorsi, and gastro-omental flaps.



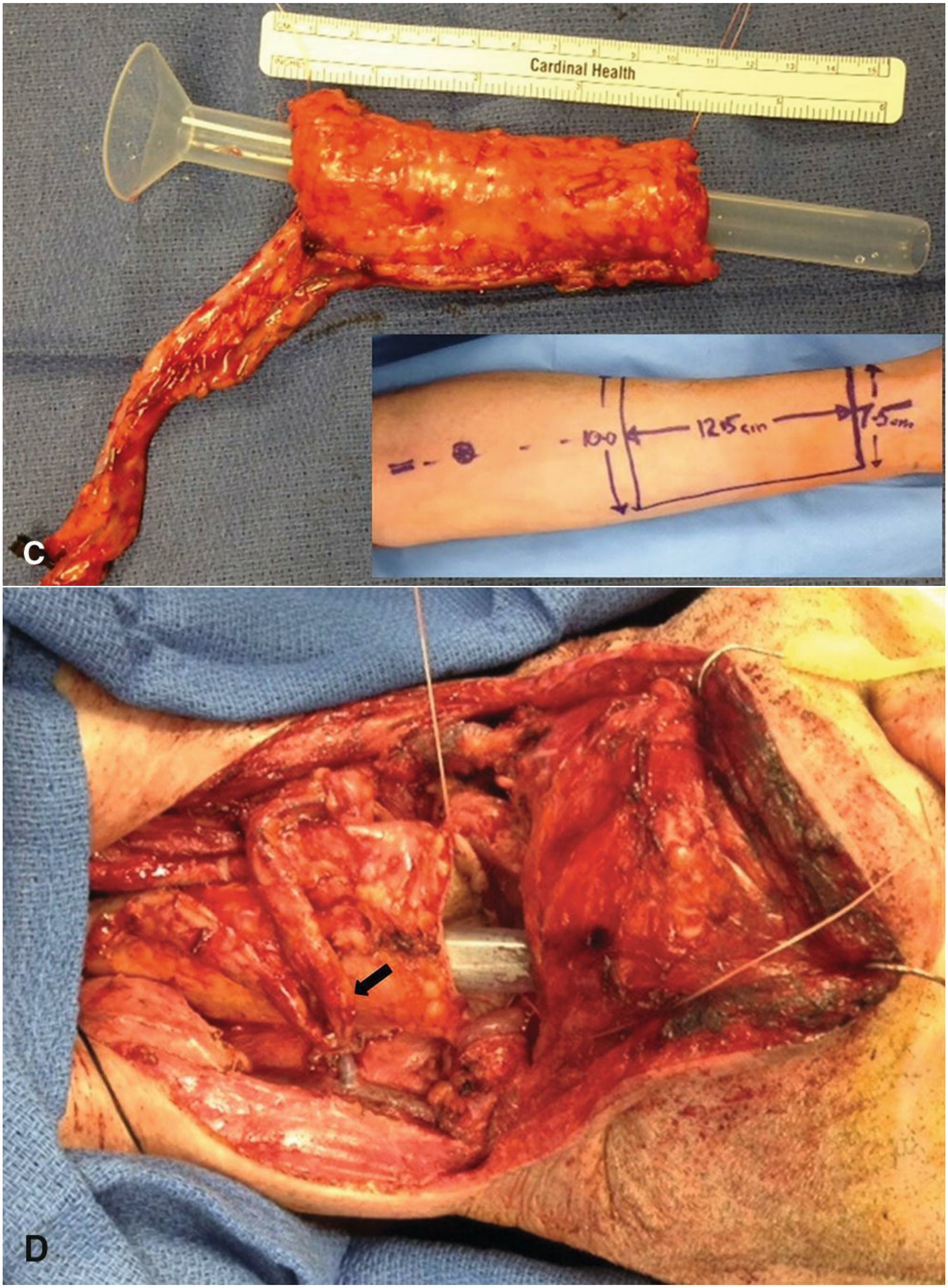

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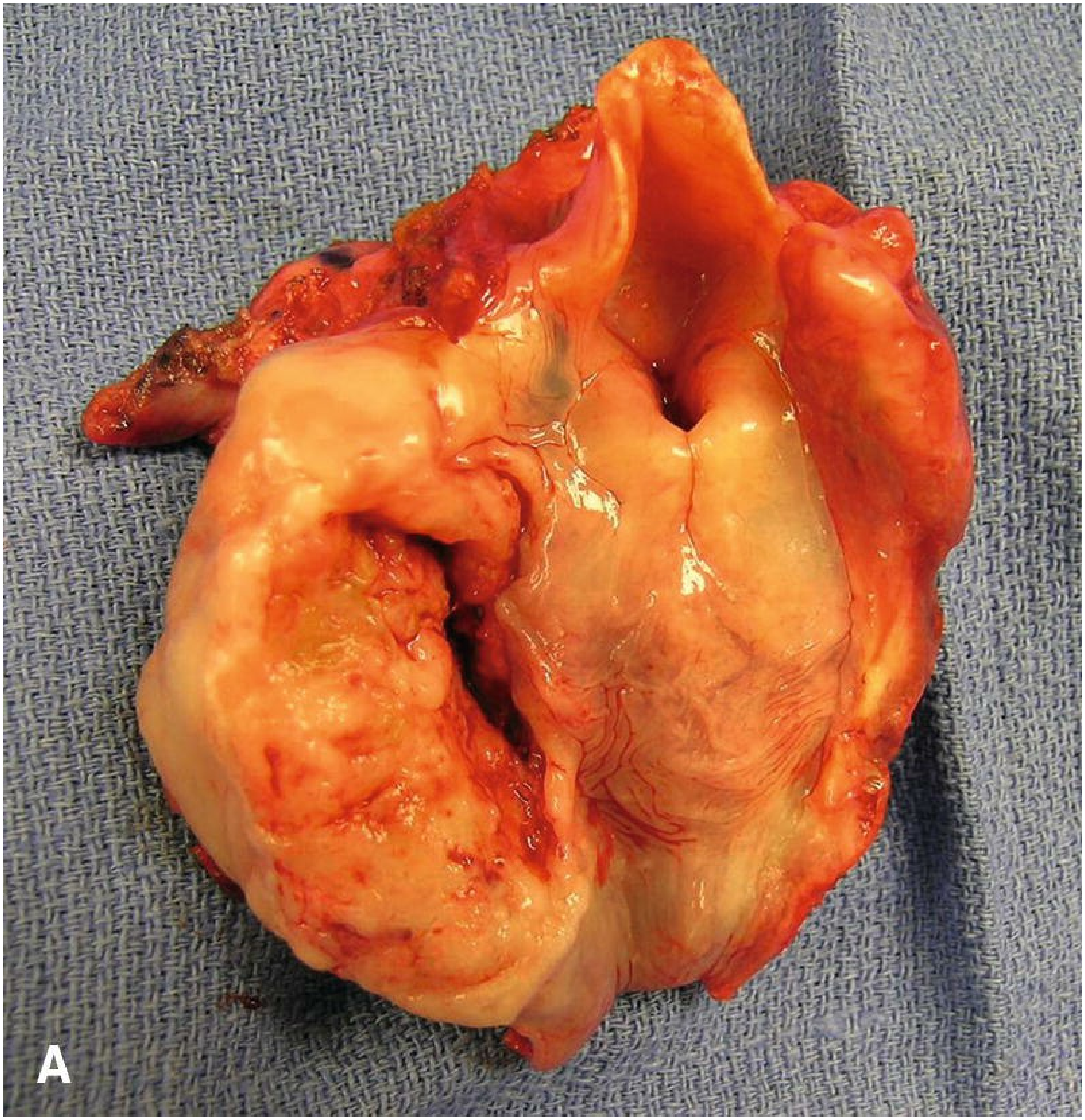
Figure 16.6. Total laryngopharyngectomy and partial esophagectomy for recurrent postchemoradiation T4 SCC of the hypopharynx and cervical esophagus. **A:** Axial CT image showing the extension of tumor at the level of cricoid cartilage **(left)** and the cervical esophagus **(right)**. **B:** Defect after primary cancer resection and bilateral level VI dissection with a partially formed tracheal stoma; the right internal carotid artery is protected by an acellular cadaveric dermal graft. **C:** Design and fabrication of a tubed radial forearm free flap (RFFF) with its vascular pedicle. **Inset** shows forearm donor site. **D:** Reconstructed pharyngoesophageal segment with tubed RFFF, salivary bypass tube traverses the neopharynx, awaiting closure, with visible external subcutaneous surface and the vascular pedicle after microanastomosis (*arrow*) on the left.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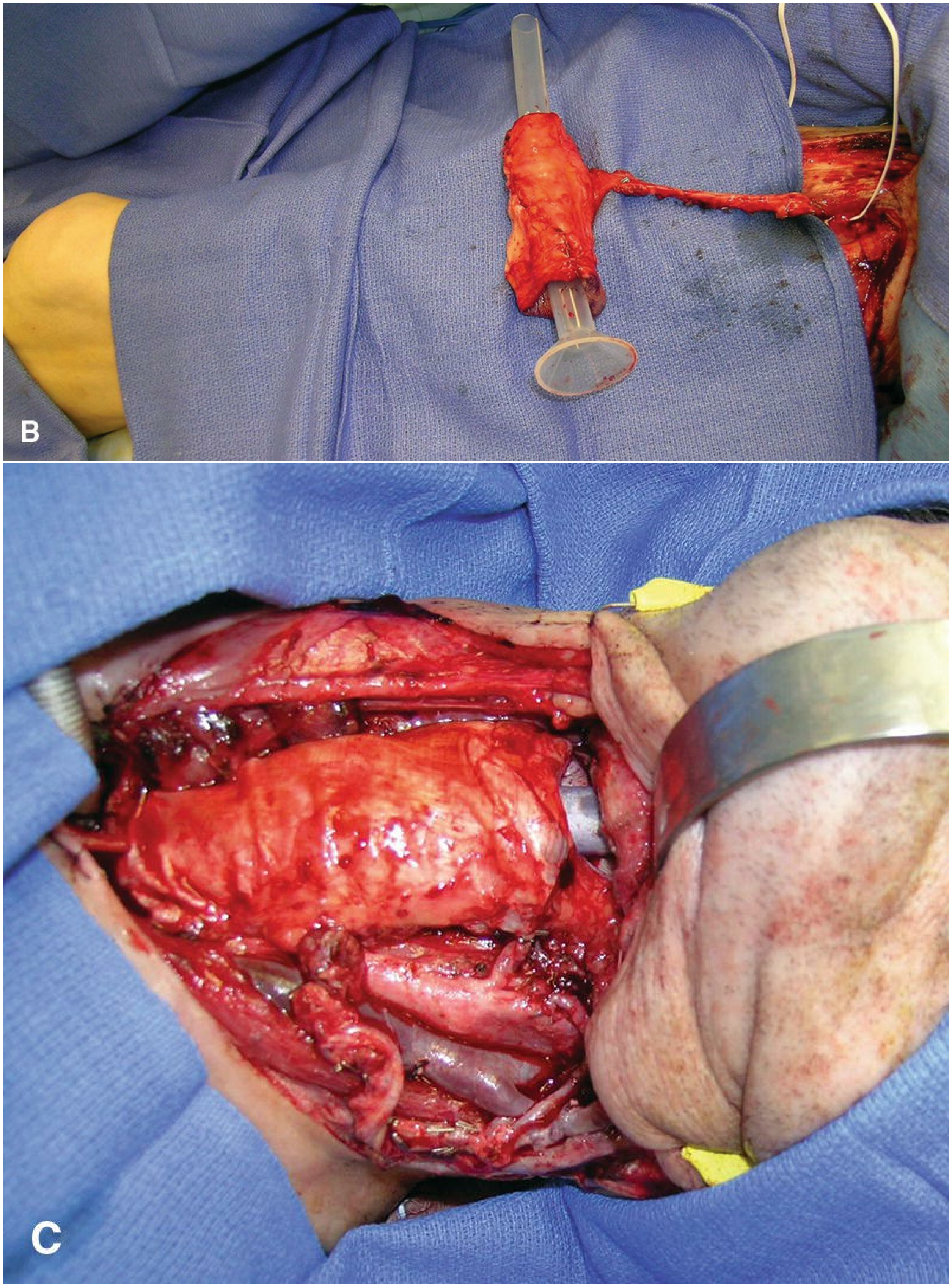
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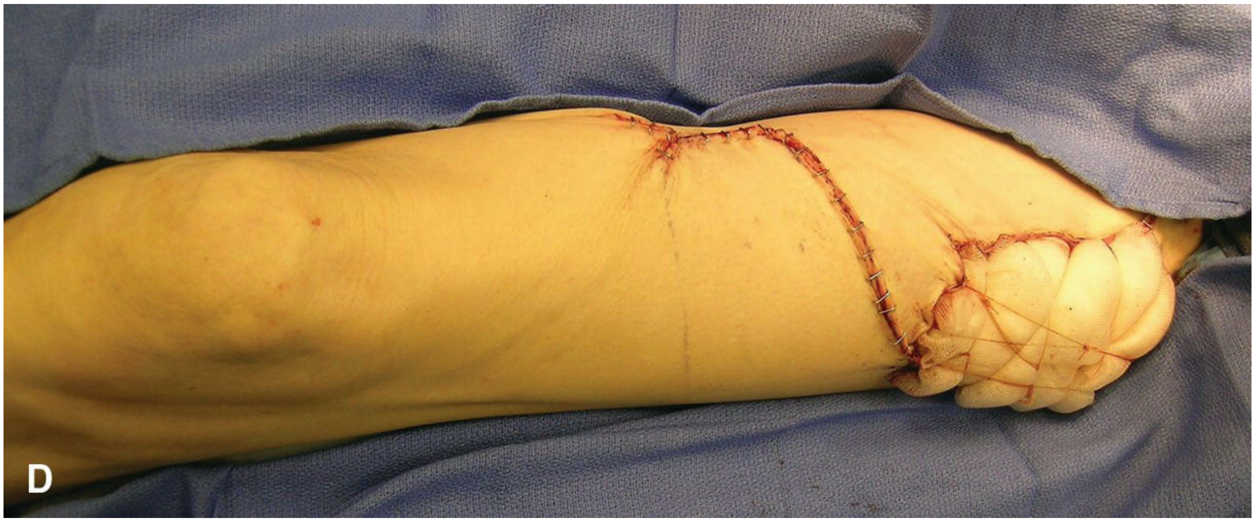

Figure 16.7. Total laryngopharyngectomy for T4 cancer of the left PFS with anterolateral thigh flap for reconstruction. **A:** Resection specimen showing a large, deeply endophytic cancer of the left PFS tumor with extension to the posterior wall of the hypopharynx. **B:** Harvested and tubed ALT flap from the left leg. **C:** Tubed ALT flap inset for reconstruction of the neopharynx. **D:** Left thigh donor site repair, requiring a skin graft (under bolster).

Total Laryngopharyngoesophagectomy

A total laryngopharyngectomy with resection of the esophagus in continuity is indicated for cancers of the hypopharynx with extension into the cervical esophagus or for a primary cancer of the upper esophagus with or without extension into the postcricoid area. A histopathologic safe resection margin of at least 4 to 7 cm is recommended for primary esophageal SCC.[35] The intrathoracic esophagus has conventionally been mobilized through the transhiatal or open thoracotomy approach, but the newer thoracoscopic mobilization has enabled a more controlled mediastinal dissection with reduced blood loss and morbidity.[7] A gastric pull-up is the reconstruction method of choice if resection of the cancer involves extensive resection of the esophagus. Gastric pull-up includes mobilization and transposition of the stomach into the thoracic cavity for restoring continuity of the alimentary tract. A tensionless anastomosis at the junction between oropharynx and stomach and a pyloromyotomy for efficient gastric drainage are crucial to prevent fistula formation and postoperative regurgitation. Colonic transposition is another reconstructive option for patients undergoing total esophagectomy.

Postoperative Management

Routine care for wound, suction drains, and tracheostomy is instituted along with perioperative antibiotics. Initiation of oral alimentation is avoided until at least 7 days after primary surgery and about 14 days in radiated patients prior to which nutritional status is maintained with nasogastric feeding. Serum protein and calcium levels are assessed and corrected as required. Intensive monitoring of flap viability is required in patients with flap reconstruction. Patients with conservation open surgery may require a PEG insertion if the aspiration is significant in order to prevent serious pulmonary complications. A trial of decannulation is usually initiated in patients with open conservation surgery after two weeks, if the airway is observed to be adequate. Decannulation may be prolonged in patients with SCHLP, as may be removal of the PEG tube.

Complications

The early complications following open surgery include hematoma in the neck, wound infection, pharyngocutaneous fistula, postoperative hypocalcemia, and flap necrosis. The most frequent late complication is varying degrees of dysphagia, which can result from neopharyngeal dysmotility or stricture formation usually at the inferior end of the neopharynx. Stomal stenosis can also occur as a late complication in patients who have had a total laryngectomy. Patients undergoing total laryngopharyngoesophagectomy are at increased risk of hemorrhage, tracheobronchial injury, and pulmonary complications such as chylothorax, atelectasis, and pneumonia. The procedure of gastric pull-up is associated with complications of anastomotic disruption or fistula; pulmonary complications such as mediastinitis, pneumothorax, and hemorrhage; and discomfort from gastric outlet obstruction-like symptoms. Necrosis and anastomotic dehiscence may also occur with jejunal autografts and colonic transposition.

Management of the Neck

A selective or modified radical neck dissection including levels II, III, IV, and VI is performed for patients with clinically positive nodes. Involvement of levels I and V are not common, hence these nodes are only included in the

dissection if indicated by the extent of metastasis to the neck.[36] Cancer of the hypopharynx is associated with a high incidence of bilateral lymph node metastases; hence, the contralateral neck is often treated on an elective basis, especially if the ipsilateral neck is pathologically positive or if the tumor extends to or crosses the midline such as those located in the medial wall of the PFS, postcricoid, and posterior pharyngeal wall. Cancer of the hypopharynx is also associated with higher contralateral occult metastasis in patients with clinically negative necks; rates up to 47% have been reported.[37] Clinically, negative necks are commonly associated with occult nodal metastases even for early (T1 to T2) cancer of the hypopharynx. An occult metastatic rate of ~50% is documented for cancers of the PFS.[38–40] Hence, a selective neck dissection including at least levels II, III, and IV is recommended in clinically negative necks. Level VI nodes should also be explored and dissected in postcricoid SCC and lesions extending to or involving the apex of the PFS and cervical esophagus.

Cancers of the posterior hypopharynx are at high risk of spread into the RPLNs. In a study[41] of 82 patients with hypopharynx and cervical esophagus undergoing RPLN dissection, metastases were reported in 16 patients (20%); 14 of these had SCC of the hypopharynx, of which 57% had involvement of the posterior pharyngeal wall. Though RPLN metastases are usually reported in cN+ necks, 15% of the patients in this study had a cN0 lateral neck. Another study[42] demonstrated that all patients with radiologically evident RPLN metastases had metastases at levels II and III; and RPLN are also strongly correlated with bilateral cervical metastases. Hence, RPLN are addressed using the approach created by resection of the primary if there is presence of radiologic evidence and dissection can be performed safely. Otherwise, they are included in the postoperative radiation field. RPLN metastases in cancer of the hypopharynx have been correlated with poor local control rates. Improved survival and reduced death from RPLN metastases after RPLN dissection has been reported in a few studies[41,43]; however, no improvement was noted in a series of 365 patients undergoing total laryngopharyngectomy with RPLN dissection.[44]

Bilateral neck dissection, including levels II to IV, VI, and the periesophageal nodes, is recommended for patients undergoing surgical resection for cancer of the cervical esophagus. Mediastinal lymphadenectomy may be required for patients with cancer of the cervical esophageal who are

discovered to have a synchronous primary cancer in the intrathoracic esophageal segment during esophagectomy.

Postoperative Therapy

The indications for adjuvant therapy following surgery include adverse pathologic features such as a T4 primary cancer, a positive or close resection margin, extracapsular spread, multiple metastatic nodes, significant extralaryngeal spread, and perineural or lymphovascular invasion. Concurrent cisplatin with postoperative radiation is recommended in patients with extracapsular spread and/or positive margins based on a pooled study of patients from RTOG 9501 and EORTC 22931 trials.[45] The hypopharynx was present as the primary site of cancer in only 10% of the RTOG[46] trial patients and in 20% of the EORTC[47] trial patients. The decision for appropriate adjuvant therapy should be made by a multidisciplinary team considering the disease status, treatment toxicity, and patient preference.

Nonsurgical Treatment

Radiation

Definitive radiation alone provides an alternative nonsurgical therapeutic option for patients with stage I and II hypopharyngeal SCC. A standard fractionation regimen involves administration of 70 to 72 Gy in fractions of 2 Gy each over 6 to 7 weeks, using the intensity-modulated radiation therapy (IMRT) or the classic three-dimensional conformal shrinking field technique. The treatment field extends from the skull base to clavicle and includes bilateral nodal basins. The dose to clinically negative nodal levels may be reduced to 50 to 56 Gy. The use of altered fractionation to intensify radiation such as hyperfractionation or accelerated regimens over conventional fractionation has been reported for stage III and IV disease.[48,49] The radiation doses and field design for primary cancers of the cervical esophagus are similar to hypopharyngeal cancer, which extends to this region; additional lymph nodes in the upper mediastinum are included in the field as required.

Chemoradiation

The two main nonsurgical treatment protocols for cancer of the hypopharynx and cervical esophagus, which use chemotherapy in combination with radiation, are concurrent chemoradiation and induction chemotherapy followed by concurrent chemoradiation. The most common chemotherapeutic agent used in concurrent chemoradiation is cisplatinum administered on days 1, 15, and 23 of radiation. The most common regimen for induction chemotherapy is a combination of taxane, platinum, and 5-fluorouracil (TPF) administered in three cycles following by concurrent chemoradiotherapy. Cetuximab, a monocolonal antibody and epidermal growth factor receptor (EGFR) blocker, is used in patients with known contraindications to cisplatinum. Radiation with cetuximab was shown to improve outcomes compared to radiation alone in a multicenter when SCC of various head and neck subsites were assessed together in a randomized trial[50]; however, the antitumor efficacy was not observed in a subgroup analysis of patients with cancer of the hypopharynx.

Complications

The most common *acute* toxicities with radiation are mucositis, xerostomia, nausea, vomiting, anorexia, dysgeusia, and dermatitis. The radiation-related adverse effects are exacerbated with the addition of cisplatin, which adds toxicities such as cytopenia, febrile neutropenia, sepsis, dehydration, hearing loss, nephropathy, and peripheral neuropathy. The most common adverse events from cetuximab include infusion reactions, acneiform skin rash, and nail disorders.[51,52]Airway edema and malnutrition may require an emergent tracheostomy and PEG insertion during the therapy. Dysphagia and aspiration from pharyngeal stenosis or esophageal stricture are the most common late toxicities of chemoradiation.[53–55] A pharyngoesophageal stricture rate of 21% was documented in a study of 199 patients treated with chemoradiation for SCC of the head and neck, the hypopharynx as the primary site was noted to be a significant predictive factor for stricture formation.[54] In another study, the feeding tube dependency rate for patients treated for cancer of the hypopharynx with concurrent chemoradiation was 31%.[55] Other long-term sequelae include cervical fibrosis, laryngeal chondroradionecrosis, and hypothyroidism. Patients may also be at risk of increased long-term toxicity with a preserved but dysfunctional larynx due to the progressive injury from chemoradiation-related nerve dysfunction,

stenosis, and fibrosis of the mucosa and muscles.[54,56–58] In patients undergoing salvage surgery for recurrent or persistent cancer after radiation or chemoradiation, higher rates of complications such as wound infection or dehiscence, pharyngocutaneous fistula, carotid rupture, and pharyngeal strictures have been observed.[59–62]

Quality of Life and Rehabilitation

Prospective evaluation of QOL outcomes has not been performed for patients with SCC of the hypopharynx who have undergone surgical versus nonsurgical treatment. However, a few studies have assessed the QOL in patients with cancer of either the oropharynx or larynx or hypopharynx treated with surgery and postoperative radiation versus concurrent chemoradiation. In the studies by El-Deiry et al.,[63] minor differences were found in favor of concurrent chemoradiation for esthetics and speech and in favor of surgery for overall QOL and avoidance of depression. In short, the overall QOL was found to be relatively well preserved in both treatment groups. In another study by Major et al.,[64] no difference between the two treatment groups was observed in patients with cancer of the larynx and hypopharynx for eight QOL domains of physical function, bodily pain, energy, health perception, social functioning, or mental health; however, patients who underwent surgery were more likely to be limited in their ability to perform activities of daily living.

For assessing the QOL in patients with cancer of the cervical esophagus, a retrospective study compared 15 patients who underwent total laryngopharyngoesophagectomy and gastric pull-up with 14 patients who received chemoradiation.[35] The posttreatment dysphagia score was significantly better for the operative group. The posttreatment QOL as assessed by a World Health Organization Questionnaire improved in both groups and was better in the operative group: however, the difference was not significant.

Speech and swallowing are critical for a good QOL; hence, rehabilitation of these functions with the assistance of a speech–language pathologist is fundamental to the management of patients with cancer of the hypopharynx, both after conservation and radical surgery as well as nonsurgical therapy. A

primary tracheoesophageal puncture (TEP) is performed for voice restoration in patients having a total laryngectomy. In patients with a total laryngopharyngectomy and tubed flap reconstruction, we recommend creating the TEP through the inlet of the esophageal stump to the infrastomal trachea, before the inferior end of the flap is anastomosed to the esophagus.[34] This maneuver eliminates periprosthesis air leakage, which in turn produces a better voice. Other methods commonly employed for voice rehabilitation include the use of electromechanical devices and esophageal speech. In patients undergoing definitive nonsurgical therapy, initiation of swallowing exercises early during the treatment, dietary modifications, and avoidance of nil-per-os (NPO) periods tend to reduce dysphagia and aspiration.[65]

Outcomes

For early cancer of the hypopharynx, high local control rates and survival have been observed with both conservation surgery and radiation when used as the primary therapeutic modality; however, no prospective comparisons have been made between the two. In a study of 101 patients with T1 to T2 cancers of the PFS treated with radiotherapy and a planned neck dissection in 43% patients, Amdur et al.[66] reported local control of 86% for T1 and 82% for T2 lesions. Late complications were noted in 12% of patients with mortality in three patients, total laryngectomy for chondronecrosis in three patients, and a gastrostomy in seven patients. Other radiation series report 5-year disease-specific survival and laryngeal preservation rates of 85% to 95.8% and 84% to 87% for T1N0 disease and 62% to 70% and 56% to 73%, respectively, for T2N0.[67,68] For T2 lesions, high volume of cancer and cancer at the PFS apex correlate with poorer local control.[69] A study by Pameijer et al.[70] reported significantly reduced 2-year local control rates if cancer volume was >6.5 mL, which roughly correlated with a tumor diameter of >2.5 cm. Survival is reported to be similar in patients treated by conservation surgery, open and transoral, ± postoperative radiation. The transoral approach has the potential to offer good disease control with fewer complications and faster recovery of swallowing.[69] Holsinger et al.[71] reported a 5-year actuarial local control estimate of 79.6% in 30 patients with T1 to T2 cancer of the PFS treated by partial pharyngectomy via lateral pharyngotomy with preoperative

chemotherapy in 8. None of the patients required neither gastrostomy nor completion total laryngectomy for functional reasons. With SCHLP for T2 PFS lesions, Laccourreye et al.[72] reported a 5-year disease-specific survival rate of 56% with a 5-year actuarial local recurrence in 3.4%; 91% of the 34 patients received induction chemotherapy, especially for T1 to T2 cancers. Local control across most TLM studies range from 72% to 90%.[73–77] A series of 23 hypopharyngeal SCC patients (T1 to T2: 70%) resected with TORS reported a 3-year disease-free survival of 84% with 96% of the patients with favorable swallowing results.[24]

For advanced hypopharyngeal SCC, the prognosis is poorer with most studies reporting the 5-year overall survival in the range of 15% to 50%, regardless of the treatment modality.[1,19] Conservation surgery of SCHLP[29] and near-total laryngectomy[78] have been applied to advanced lesions with good local control and survival, but the techniques may be challenging. Five-year actuarial local control of 93% in T3 and 63% in T4 PFS SCC has been reported by Laccourreye et al. using SCHLP; a majority of cases also received induction chemotherapy.[29] Five-year survival of ~66% with high local control has been reported for cancer of the hypopharynx treated with near-total laryngectomy.[78,79] The outcomes with TLM for advanced T3 to T4 cancers is favorable with diligent case selection, although the experience is limited to a few institutions. Vilaseca et al. reported a local control rate of 67% for T3 cancers (*n* = 6/9).[74] Martin et al.[80] reported 5-year Kaplan Meier local control rates of 75% for T3 and 57% for T4 cancers. For the entire series of 172 patients, they reported a 5-year recurrence-free survival of 73% for stages I to II, 59% for stage III, and 47% for IV. Laryngeal function was preserved in all but one. Six patients had permanent gastrostomy tubes.[80]

Randomized trials have been conducted to assess the outcomes of radical surgery versus nonsurgical combined therapy with chemoradiation. The EORTC 24981 multicenter study randomized 194 T2 to T4 patients with cancer of the hypopharynx (T2, 19.5%; T3, 75%; T4, 6%) patients to total laryngectomy or induction chemotherapy followed by radiation and reported similar10-year progression-free survival in the two arms (8.5% in surgery and 11% in induction RT arm) and a laryngeal preservation rate of 8.7%.[81]Another trial of 92 patients with T3 to T4 cancer of the hypopharynx randomized to surgery or radiation alone following neoadjuvant chemotherapy reported better 5-year overall survival (37% vs. 19%) and local

control (63% vs. 39%) in the surgical versus RT arm.[82] In an epidemiologic study of 595 patients (T1 to T2: 46%; T3 to T4: 54%), Hall et al.[83] demonstrated that there was no difference in overall survival or cause-specific survival after surgery ± postoperative radiation or definitive RT ± salvage surgery. These data were analyzed using three techniques: a restricted cohort study (patients with only resectable disease), a matched case study (for the criteria of T stage, N stage, and performance score), and a natural experiment study (based on geographical differences in treatment practices). None of the three methods revealed a difference in survival.[83]

For recurrent cancer of the hypopharynx in patients originally treated with radiation or chemoradiation, salvage surgery can achieve locoregional control if performed as a timely intervention in selected patients, but usually, the recurrent cancer is advanced resulting in low survival with frequent perioperative complications rates. Five-year survival across different studies varies from 18% to 23%.[84–86]

Due to the rarity of cancer of the cervical esophagus, large series reports on treatment outcomes are sparse. The reported 5-year survival outcomes with either radical surgery and adjuvant therapy or nonsurgical therapy in patients treated with curative intent are similar and range from 15% to 40%.[7,87] Dysphagia and aspiration pneumonia are common posttreatment sequelae and have been reported to be more common with nonsurgical approaches, whereas voice is a problem with surgically treated patients.[35]

Thus, based on the available studies reporting disease outcomes with different therapeutic strategies, there is no strong evidence to support one curative treatment over another. Direct comparison of patient function and QOL using uniform validated instruments is also lacking. Therefore, it is important that the therapeutic decision is made by a multidisciplinary team in the best interest of the needs and preferences of the patient in order to optimize the cure, function, and QOL and minimize treatment-related morbidity and mortality.

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17 Tumors of the Cervical Trachea

Ralph W. Gilbert Shaf Keshavjee

Primary tumors in the trachea are relatively uncommon, with an estimated 2.7 new cases per million per year. The rarity of these tumors and their subtle clinical presentation require surgeons to have a high index of suspicion particularly with specific clinical presentations. Patients with a tumor of the trachea will present with a range of symptoms, including dyspnea on exertion and inspiratory wheezing, with a normal chest radiograph. Frequently, these patients will be diagnosed and treated as adult-onset asthma long before further investigations determine the presence of an obstructing tumor of the trachea.

This chapter will review the surgical anatomy of the cervical trachea, clinical presentation and diagnostic evaluation of patients with tumors of the cervical trachea, and anesthetic and surgical approaches to both resection and reconstruction of the cervical trachea. It will also review the role of nonsurgical organ preservation approaches and the role of adjuvant therapy in the management of malignant tumors of the upper airway.

The surgical approach to tumors involving the cervical trachea differs from the approach used for tumors of the distal trachea or carina. Although this chapter is directed toward the special problems of the cervical trachea, generalizations must be made from the total experience with tumors of the trachea.

Surgical Anatomy of the Trachea

The trachea begins at the lower border of the cricoid cartilage and terminates where the lateral walls of the right and left main bronchi flare out from the lower trachea. The carinal spur is useful as a definite landmark for the termination of the trachea because it is clearly seen both bronchoscopically and radiologically. The average adult human trachea measures 11 cm in

length with slight variation in proportion to the height of the individual.[1] There are approximately two tracheal cartilaginous rings per centimeter of trachea. With the exception of congenital tracheal stenosis with circumferential rings of the trachea, the cricoid is the only completely circular cartilage in the upper airway.

Direct access to the trachea in the neck is of critical importance both for surgical access and for ease of reconstruction following resection. In young people, hyperextension of the neck frequently delivers in excess of 50% of the trachea into the neck.[2] However, in an aged, kyphotic individual, even the most vigorous hyperextension may fail to deliver any of the trachea into the neck. The anatomic position of the trachea changes from an essentially subcutaneous position at the level of the cricoid to a prevertebral position at the level of the carina; thus, the course of the trachea is normally caudad and dorsal.

The blood supply of the trachea is of critical importance in resection and reconstruction of the trachea. The upper trachea is supplied primarily by branches of the inferior thyroid artery, and the lower trachea is supplied by branches of the bronchial artery, with contributions from the subclavian, supreme intercostal, internal thoracic, and innominate arteries. These vessels provide branches anteriorly to the trachea and posteriorly to the esophagus. They have a perforating pattern that arrives at the trachea from its lateral aspect. The longitudinal anastomoses between these vessels are fine, and transverse intercartilaginous arteries branch ultimately into a submucosal capillary network.[2–4] Excessive division or dissection of these lateral perforators during circumferential dissection of the trachea risks disruption of this network and may lead to devascularization of trachea segments and a failed anastomosis.

The trachea is also intimately related to several critical structures. These include the recurrent laryngeal nerves, the esophagus, and the thyroid gland. Detailed knowledge of these anatomic relationships is essential before attempting any ablative or reconstructive surgery on the cervical trachea.

Evaluation of Patients

Symptoms of a tumor in the trachea, even in the presence of a high degree of airway obstruction, may be insidious. Most commonly, patients with a tumor

in the trachea present with any of dyspnea, hemoptysis, cough, wheezing, dysphagia, change hoarseness, stridor, and pneumonia. In one series, productive cough and shortness of breath were the most common symptoms. A history of slowly progressive dyspnea on exertion is often present.[5] Many patients with a malignant neoplasm will present with hemoptysis often leading to an appropriate bronchoscopic diagnosis. An irritative cough, which may or may not be productive and which may in time be associated with hemoptysis, is sometimes also seen. Change in vocal quality as a result of involvement of one or both recurrent laryngeal nerves is not uncommon and may be insidious in onset. Stridor as a presenting symptom is often reflective of a late presentation of disease. All too often, especially with slowly growing tumors such as adenoid cystic carcinoma, the patient who has developed slowly progressive shortness of breath and wheezing will have an apparently normal chest radiograph. This leads to the diagnosis of adult-onset asthma, with some patients treated with steroids for a prolonged period of time before the slowly growing tumor is discovered.

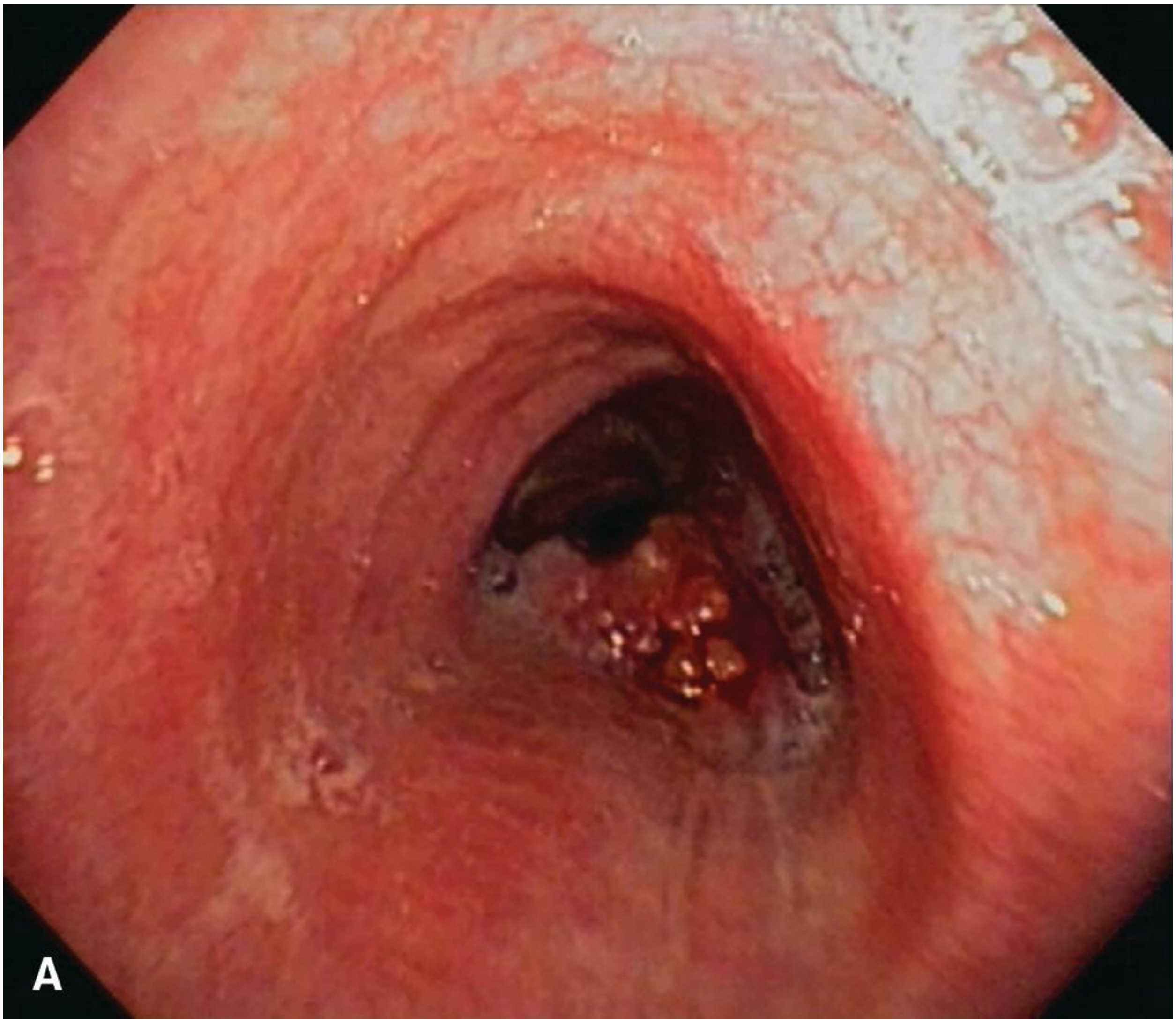
In general, the more aggressive tumors are diagnosed earlier owing to their propensity to present with prominent symptoms, for example, hemoptysis. In one study, the mean duration of symptoms before diagnosis in patients with squamous cell carcinoma (SCC) of the trachea was 4 months, whereas the mean duration of symptoms before diagnosis in adenoid cystic carcinoma of the trachea was 18 months.

Diagnostic Studies

The primary diagnostic modalities for delineating tracheal abnormalities are radiologic studies and laryngoscopy and bronchoscopy.

The following investigations are helpful:

1. Chest radiograph (posteroanterior, lateral, and oblique) centered high enough to obtain good views of the trachea.
2. Computed tomography (CT), with multiplanar reconstruction is the gold standard for assessing extent of disease and defining extratracheal involvement as well as detecting the presence of lymph node involvement[6] (Fig. 17.1A and B).
3. Three-dimensional reconstructions from CT can be useful in visualizing and planning surgery (Fig. 17.2A and B).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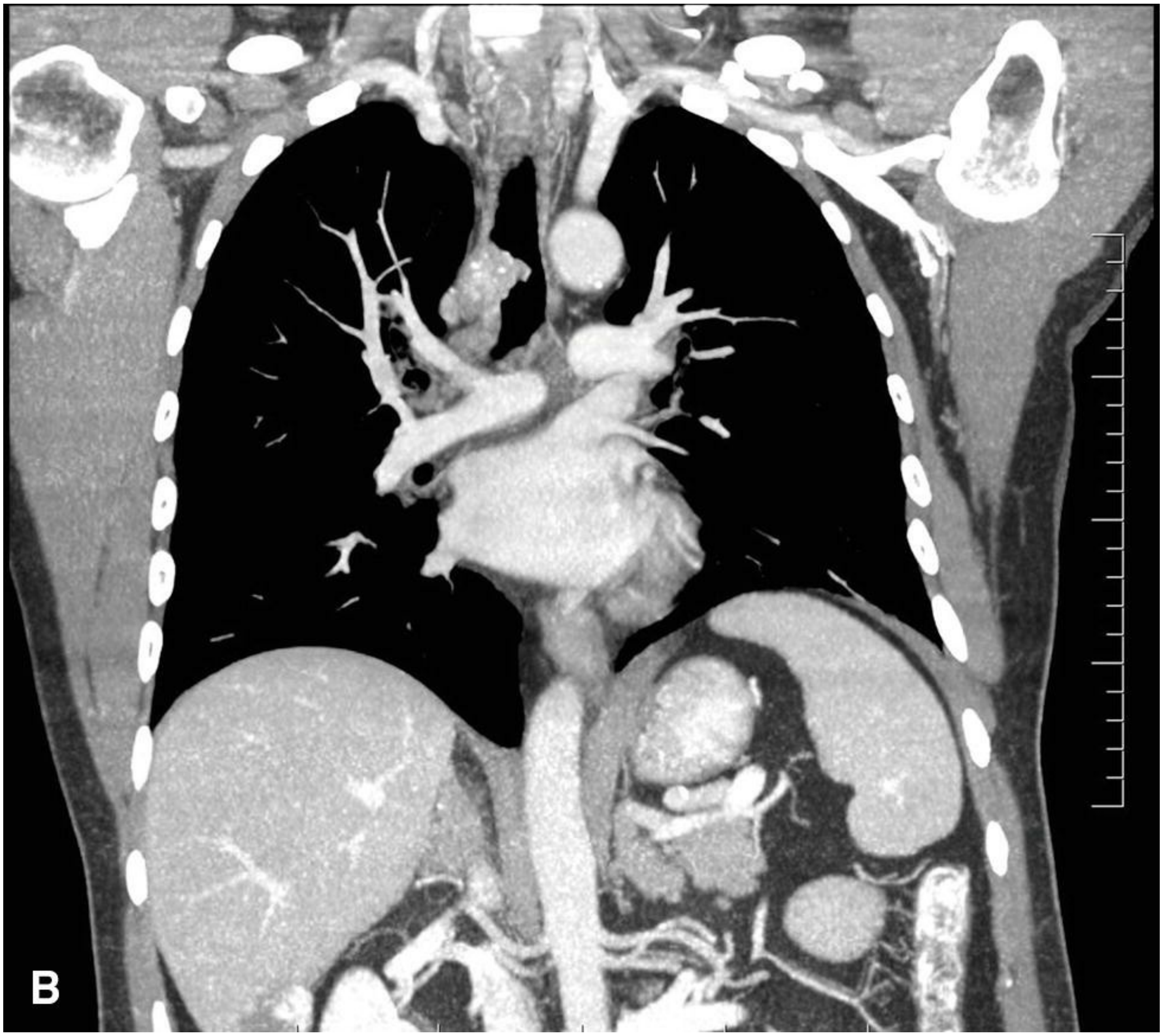
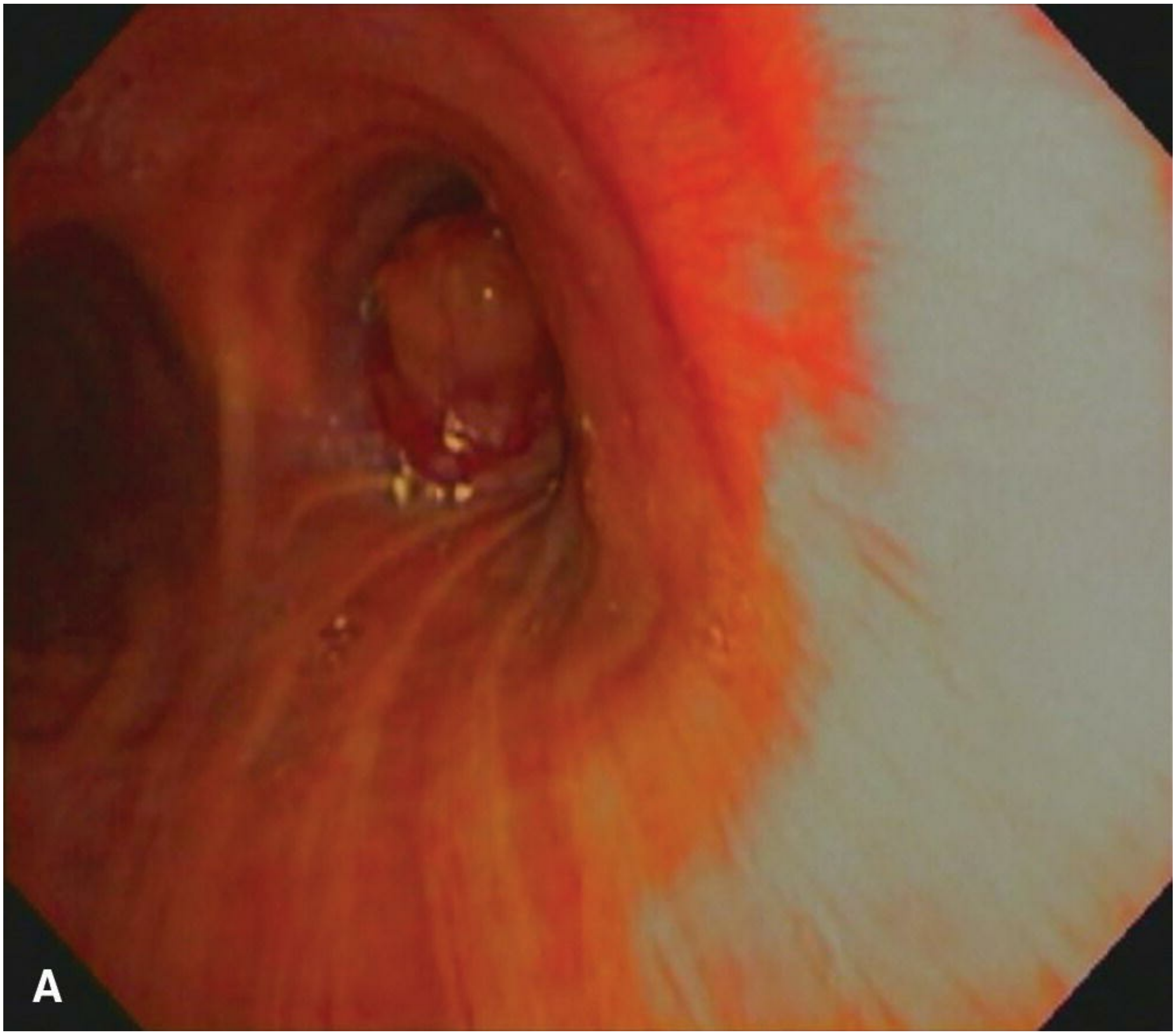


Figure 17.1. CT imaging of tracheal SCC including endoscopic view **(A)** and coronal CT **(B)**.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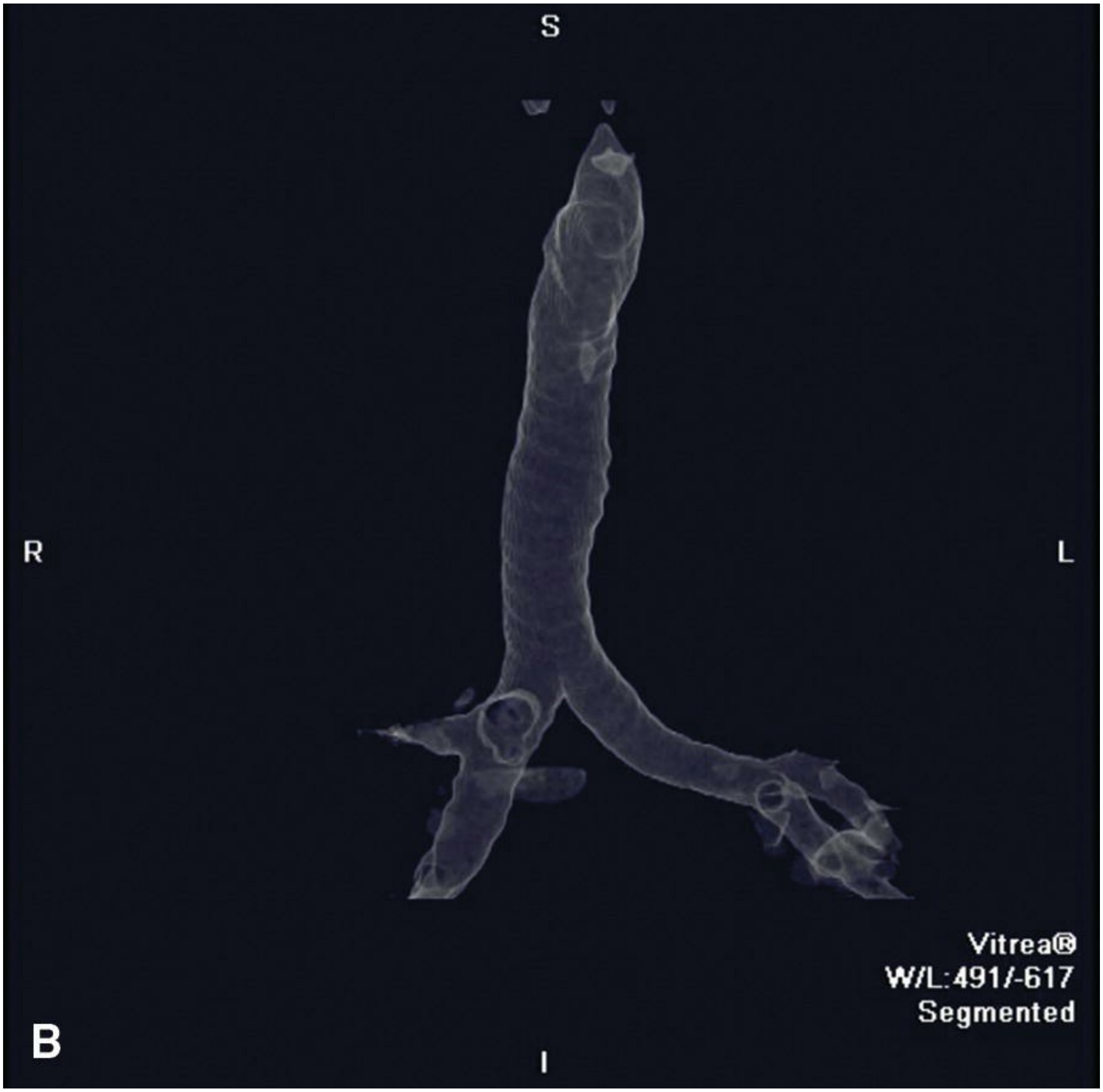

Figure 17.2. Endoscopic **(A)** and virtual endoscopic **(B)** views of tracheal tumor.

Barium esophagram may demonstrate esophageal involvement by extrinsic compression and/or invasion. Magnetic resonance imaging offers the advantage of soft tissue delineation of the trachea; however, it offers little advantage over CT.

Functional studies are of limited usefulness. They may, at times, call attention to an obstructing lesion when clinical signs and symptoms are subtle. Functional studies may also give information about the status of the

lung parenchyma.

All patients suspected of having or known to have a tumor of the trachea require endoscopy at some point during their evaluation. Great caution must be taken with the use of flexible laryngoscopy and bronchoscopy in these patients. Instrumentation of a nearly obstructed trachea may lead to bleeding, edema, or increased secretions that may precipitate sudden airway compromise. No effort should be made to employ instrumentation or to pass beyond a tumor if there is a high degree of obstruction unless preparations have been made to proceed directly with surgical intervention. It is preferable to simply identify the presence of the tumor and to defer any further evaluation and biopsy until appropriate arrangements have been made to manage the airway in the event of problems.

In general, the rigid bronchoscope is preferred when tumors of the trachea are studied. The need to establish an airway by tumor debulking or to obtain more adequate biopsy for diagnosis by frozen section justifies the use of the rigid bronchoscope (with appropriate magnifying telescopes). If necessary, the flexible bronchoscope may be passed through the rigid instrument for the evaluation of disease distal to the main obstruction. Careful measurements must be taken to determine the extent of tracheal involvement as well as to determine the amount of trachea remaining for reconstruction. It is important to establish the distance from the vocal cords to the superior aspect of the tumor, the length of the lesion, and distance from the inferior extent of the mucosal changes to the carina to facilitate surgical planning.

Histology and Staging of TUMORS OF THE TRACHEA

The common primary neoplasms of the trachea are listed in Table 17.1. The majority of tumors are either SCC or adenoid cystic carcinoma with SCC representing ~50% of the histology in most series. Other less common tumors include adenocarcinoma, carcinoid, or neuroendocrine and other rare tumors including sarcoma.

Table 17.1 Histology

Histology	Urdaneta[24]	Regnard[9]	Webb[18]
SCC	45%	52%	46%
ACC	16%	36%	26%
Small cell (neuroendocrine)	9%	5%	8%
Adenocarcinoma	6%	5%	8%
Large cell carcinoma	4%	ns	5%
Sarcoma	4%	1%	2%

Tumors are staged according to the AJCC staging system, which is illustrated in Table 17.2.[10]

Table 17.2 AJCC Staging[6]

	Definition
T Stage	
T1	Primary tumor confined to the trachea; size <2 cm
T2	Primary tumor confined to the trachea; size >2 cm
T3	Spread outside the trachea but not to adjacent organs or structures
T4	Spread to adjacent organs or structures
Tx	Unknown or cannot be assessed
N Stage	
N0	No evidence of regional nodal involvement
N1	Positive nodal involvement
Nx	Unknown or cannot be assessed

Presentation

Primary SCC of the trachea may present as an exophytic mass that is circumscribed or as a spreading lesion that involves a considerable length of the trachea. It may also present as an ulcerative lesion. The cancer may grow into the mediastinum and may be noted radiographically as a bulky extratracheal mass. Metastases to paratracheal and subcarinal lymph nodes as well as direct invasion of mediastinal structures may also occur. This cancer occurs predominantly in males, and the majority of patients will have a smoking history.

Adenoid cystic carcinoma may present as an exophytic mass, frequently with poorly defined margins. A bulky extratracheal mass may be present. In the cervical trachea, the thyroid gland may be directly invaded as well as the

esophagus. It is extremely unusual for adenoid cystic carcinoma of the trachea to present with regional lymph node metastases; if present, it suggests a high-grade subtype of this cancer. This tumor is histologically characterized by submucosal extension and perineural invasion over long distances of the trachea. The submucosal extent is often not visible, even after transection of the trachea. Frozen section control during surgery is critical, and the extent of the cancer may present the surgeon with a problem not predictable preoperatively. The hallmark of this cancer is frequent, and late presentation of metastases to the lungs is sometimes 5 to 10 years following presentation.

The group of miscellaneous cancers includes a wide variety of cancers of varying malignant potential.

Airway Management

Adequate control of the airway is of critical importance in the management of all tumors of the trachea. Tumors of the trachea may present with airway obstruction, and endotracheal intubation may prove impossible. Control of the airway is best accomplished in the operating room, where an assortment of rigid bronchoscopes, dilators, biopsy forceps, and instruments for emergency tracheotomy are available. The key element in safe airway management of these challenging patients is a close collaboration between the anesthesiologist and the attending surgeon. The plan for anesthesia, airway instrumentation, and postprocedural airway management should be discussed prior to the induction of anesthesia.

Anesthesia

Anesthesia for upper airway obstruction remains controversial.[11] Essentially, there are two approaches, inhalation induction with sedation or intravenous induction with administration of neuromuscular blockade. The traditional technique has been an inhalational induction with sevoflurane. Proponents of this technique believe that its major advantage is the maintenance of spontaneous ventilation, theoretically avoiding the risk of sudden loss of the airway. In clinical practice, however, when a patient with a severely obstructed airway undergoes an inhalational induction, the induction is slow, there are periods of apnea, and the patient often becomes hypoxic and hypercarbic. When inhalational induction fails, the anesthetic and surgical

team will have to revert to intravenous induction and neuromuscular blockade to maintain ventilation. The nontraditional technique and the one currently advocated by experienced airway teams are intravenous induction and neuromuscular blockade; these techniques accelerate induction and allow airway instrumentation while maintaining the ability to maintain ventilation. No single technique is perfect, and anesthesiologist faced with an upper airway obstruction need to use both techniques depending on the clinical experience of the team and its ability to instrument the airway.

Clinical Endoscopy

Initial evaluation should be done with a rigid bronchoscope carefully inserted through the vocal cords, stopping just proximal to the level of obstruction. Rigid telescopes may then be inserted through the bronchoscope to assess the degree of obstruction. A rigid bronchoscope can be passed beyond most tumors, even those causing near-complete airway obstruction. Once the status of the distal airway has been assessed, partial removal of the tumor with biopsy forceps can be done in order to determine its consistency and vascularity. For the vast majority of tumors, the tip of the rigid bronchoscope can be used to “core out” most of the tumor; the tumor may then be grasped with the biopsy forceps and removed. If bleeding is noted in the airway, the bronchoscope can be passed into the distal airway, thus ensuring adequate ventilation as well as serving to tamponade the bleeding. Epinephrine irrigation through the flexible or rigid bronchoscope can be effective in producing vasoconstriction and reducing bleeding. Rarely, cautery (with insulated suctions) may have to be used. The use of the YAG laser has become increasingly popular in the management of tumors obstructing the airway, as well as in coagulation of bleeding sites. Endotracheal removal of malignant tumors, either mechanically or by other means, is clearly a temporizing maneuver. However, the use of such techniques in emergent situations may allow for further evaluation of the patient in a relatively elective setting and allow for the appropriate surgery to be performed in an elective manner.

Treatment Selection

Treatment of Benign and Low-Grade Lesions

There is no question that the best treatment for a benign tumor of the trachea is complete surgical extirpation with primary end-to-end reconstruction.[12,13] This is almost always feasible for benign lesions, even if they are relatively extensive. Complete removal by circumferential segmental resection is likely the simplest approach. Occasionally, a surgeon is tempted to consider lateral resections; these may be indicated in selected patients with nonluminal involvement.

Tracheal resection and reconstruction have limited application for tumors that involve the trachea secondarily. When the primary tumor is localized and is a low-grade malignancy (e.g., papillary thyroid carcinoma), tracheal resection is indicated and is highly effective. The detailed management of thyroid cancer is discussed separately in this textbook; however, a recent publication suggests that with a variety of resection techniques and adjuvant radiotherapy, overall survival in this population of patients is 79% and 71% at 3 and 5 years, respectively.[14]

Treatment of Advanced Disease

Numerous options exist in the primary treatment of malignant tumors of the cervical trachea. Investigations and staging will establish whether a tumor is resectable or not. Generally, resectability includes patients with tumor involving <50% of the length of the trachea without significant involvement of extratracheal structures including the esophagus and mediastinal structures. In the setting of a resectable lesion, the primary treatment options include primary surgery alone, surgery and postoperative radiotherapy or chemoradiation, and primary chemoradiation without surgery. Neoadjuvant or preoperative radiotherapy is usually not indicated as it may compromise wound healing, a particularly important issue in the setting of trachea resection.

Whereas the evidence of quality is poor (level III), the consensus of published series suggests that for resectable lesions, primary surgery and adjuvant radiotherapy or chemoradiation in SCC of the cervical trachea and primary surgery and adjuvant radiotherapy in adenoid cystic carcinoma be considered.[8,9,12,15–18] Patients with adenoid cystic carcinoma can be challenging as these cancers may infiltrate submucosally and frequently exhibit perineural extension often making margin status problematic. In

patients with adenoid cystic carcinoma, the degree of radicality needs to be evaluated carefully. This group of patients will have a long survival and a high rate of distant metastases regardless of margin status. Inflicting significant surgical morbidity or risk of perioperative mortality needs to be considered in the context of probability of long-term survival.

In the patients who have unresectable cancer, most advocate primary radiotherapy or concomitant chemoradiation usually with cisplatinum-based chemotherapy protocols. A few series have reported complete responses in advanced cancers; however, the numbers of patients treated is extremely small.[19–22]

Prognostic factors predictive of disease-free survival and overall survival include resectability, margin status, nodal involvement, histology, and the use of adjuvant radiotherapy. Margin status is particularly important in SCC of the trachea along with the presence of nodal metastasis. Controversy exists over the importance of clear margins in adenoid cystic carcinoma with some authors showing significant impact on locoregional control and survival and others suggesting a less dramatic effect.[7,8]

Surgical Technique

The surgeon should have a comprehensive understanding of the techniques of management of the entire upper airway, including experience with flexible and rigid endoscopic techniques, various release maneuvers, and ways to obtain a tension-free anastomosis and an experience and understanding of the stenting options for the upper airway. The surgeon must know the blood supply of the trachea, the course of the recurrent laryngeal nerves, and the options for reconstruction. Each case must be carefully studied and each operation carefully planned before such a procedure is undertaken.

Positioning and Incision

The patient should be positioned to allow full access to the operative field. This usually means neck extension using an inflatable placed as a shoulder bolster. A low-collar incision is used for tumors located in the upper half of the trachea (Fig. 17.3). This incision may be extended through the upper portion of the sternum if access to the mediastinal trachea as required. Exposure of the larynx is obtained by carrying the flap elevation to the level

of the hyoid. If the tumor appears to be extensive, as is sometimes the case with adenoid cystic carcinoma, the patient should be positioned in a manner that allows extension of the incision into the right fourth interspace to the posterior axillary line. Some thoracic surgeons will free drape the right arm so that it can be moved back and forth as necessary.

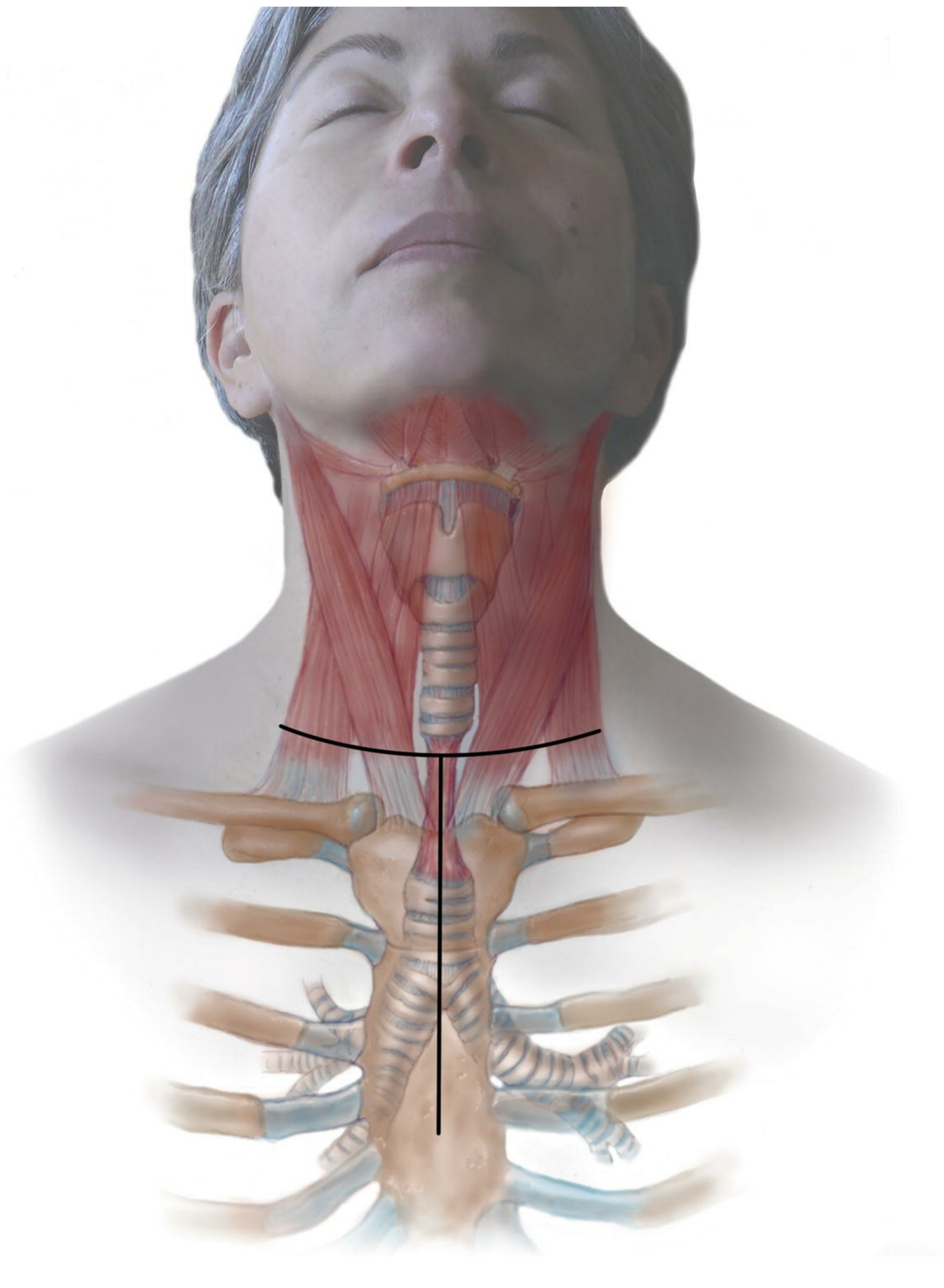

Figure 17.3. Incision design tracheal resection.

Resection

The surgical approach for benign tumors of the trachea varies somewhat more than that for malignant tumors. For benign tumors, dissection is maintained adjacent to the trachea; in this approach, which is similar to tracheal or cricotracheal resection, the recurrent nerves are not visualized. This approach is safe as long as the plane of dissection is maintained directly on the surface of the trachea.

When malignant tumors are resected, the recurrent laryngeal nerves are identified at a distance from the cancer and are followed toward the area of the cancer. It may be necessary to sacrifice a recurrent laryngeal nerve on the side of the tumor due to its involvement with the tumor. Adjacent lymph nodes should be included in any dissection for a malignant tumor. However, such a dissection should be limited because it may endanger the blood supply of the trachea. A compromise must be made between the potential of leaving behind paratracheal tissue that may contain positive lymph nodes and avoiding devascularization of the trachea. Circumferential dissection of the trachea over a great distance should be avoided because this may endanger the blood supply and can lead to problems with healing and/or stenosis. It is best not to circumferentially free more than 1 to 2 cm of trachea from the point at which the trachea is to be transected.

Once the trachea has been identified, the entire pretracheal plane is freed bluntly to the carina and often down the proximal anterior surfaces of the mainstem bronchi. Care is taken to spare the lateral pedicles because these contain the blood supply to the trachea. Isolation of the portion of the trachea containing the cancer is begun on the side of the trachea away from the cancer, and an effort is made to include appropriate lymph nodes. Once the inferior-most extent of the cancer is identified, preparations are then made for transection of the trachea. A sterile anesthetic circuit is passed to the anesthesiologist, and a sterile cuffed endotracheal tube is brought into the operative field. The trachea is then opened in a transverse manner immediately distal to the inferior aspect of the cancer, and the lumen is carefully inspected. If it seems that the division will occur at an appropriate level, the transection is completed; if the level is inappropriate, a more distal level is chosen under direct vision.

After transection of the distal trachea, the airway is intubated across the field with the flexible endotracheal tube. At this point, the orotracheal tube may be withdrawn to a level proximal to the anticipated proximal extent of tumor; it is wise to place a suture to the tip of the tube so that if it is withdrawn above the vocal cords, it may be reintroduced with ease at the end of the case. A small portion of tracheal tissue distal to the line of transection is removed and sent for frozen section analysis so that the adequacy of the distal margin can be determined.

The transected end of the trachea is now grasped with forceps and is placed on gentle traction to facilitate proximal dissection. The esophagus is usually left intact. However, it may be necessary to include a full-thickness segment of the anterolateral wall of the esophagus; at other times, only the muscularis may be excised. Any defect in the esophagus is repaired primarily in two layers with fine interrupted sutures and is reinforced with autologous tissue such as a strap muscle.

With the dissection carried proximally, the proximal extent of the cancer is identified from within the tracheal lumen, and a point of transection is chosen. At times, it may be necessary to bevel obliquely a portion of the inferior aspect of the larynx, such as half or more of the cricoid cartilage, to obtain an adequate proximal margin. Once the proximal point of transection is determined, traction sutures are placed in the proximal trachea in a manner similar to those placed distally, if the transection point is relatively high, the sutures may be placed in the larynx. The trachea is then transected, and a specimen is submitted for frozen section analysis of the proximal margin.

Reconstruction

After removal of the specimen and after establishment of clear margins of resection both proximally and distally, reconstruction can begin. The anesthesiologist is asked to temporarily flex the neck as the surgeon and assistant simultaneously draw together the traction sutures on each side of the trachea. Gentle traction on the sutures should approximate the two ends of the trachea. If excessive tension is noted, release maneuvers will need to be considered. Excessive tension on the anastomosis markedly increases the likelihood of separation or stenosis, both potentially disastrous complications. If further relaxation is deemed necessary to avoid excessive tension, a variety of release maneuvers may be used. The suprahyoid laryngeal release is

particularly effective, especially after resection of the proximal trachea. This maneuver usually obtains an additional 1 to 2.5 cm of tracheal length proximally, but it is of limited use in resection of the distal trachea or carina. Other maneuvers may be performed, but they require entry into the thoracic cavity. These include mobilization of the inferior pulmonary ligament, intrapericardial release of the right hilum, and, rarely, bronchial transplantation.

Once it has been demonstrated that tracheal approximation can be obtained without excessive tension, the neck is again extended and the anastomosis completed. The anastomosis is performed with a absorbable 4-0 monofilament suture. The use of absorbable suture material has dramatically reduced the incidence of suture line granulomas, a problem that was encountered with the use of nonabsorbable suture. Our approach is to place two stay sutures at the posterior edge of the cartilaginous trachea and then close the back wall with a running 4-0 suture. The stay sutures are tied and the back wall suture tensioned and tied to the stay sutures on each side (Fig. 17.4).

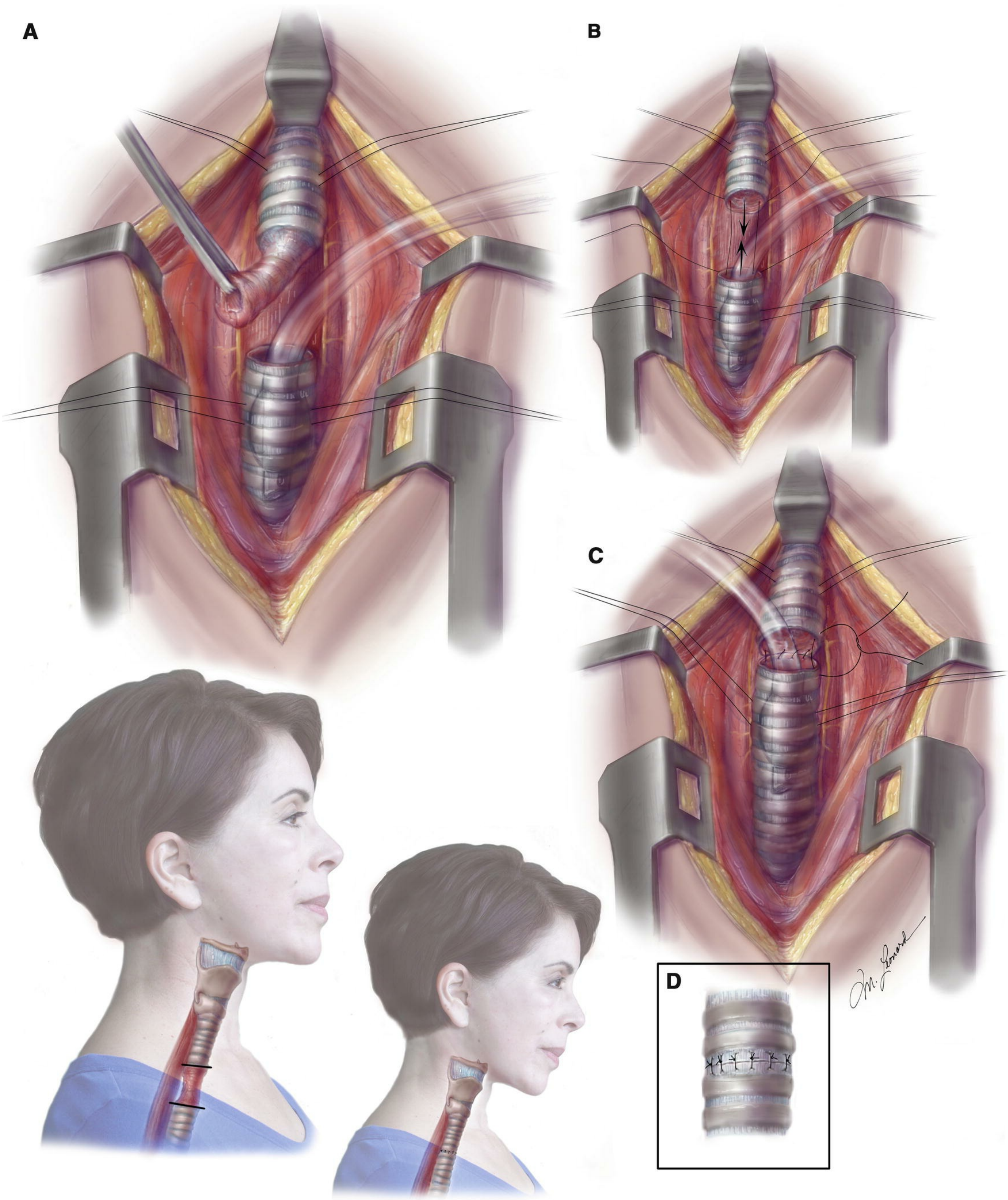

Figure 17.4. A–D: Circumferential cricotracheal resection.

The endotracheal tube is removed from across the operative field, and the orotracheal tube is once again advanced and placed into the distal airway under direct vision. The remaining anterior wall sutures are then placed in an

interrupted fashion. If the thyroid isthmus is intact, the isthmus may be sutured over the anastomosis. Although it is not necessary to interpose a pedicled strap muscle between the innominate artery and the anastomosis, some surgeons may wish to do so to add a measure of security.

Suction drains are placed in the substernal and/or paratracheal areas, and the incision is closed in layers. A heavy suture (Grillo stitch) is placed from the crease below the chin to the presternal skin. This serves as a guardian suture in the postoperative phase, reminding the patient not to suddenly hyperextend the neck. The suture is usually removed on postoperative day 5. Except in rare circumstances, every effort is made to extubate the patient at the conclusion of the operation. In patients with high tracheal or cricoid cancers where a cricotracheal resection has been performed, some authors advocate the use of silastic T-tubes. These tubes are usually positioned with the proximal limb just above the vocal cords with the external limb exiting the trachea one to two rings below the repair through a small tracheotomy. T-tubes have a role in patients at risk of supraglottic edema and potential airway obstruction and where the quality of the proximal or distal trachea is in question. We usually remove the T-tube 4 to 6 weeks postoperatively.

Postoperative Care

Throughout the performance of tracheal resection and reconstruction, care is taken to avoid the entry of blood and secretions into the tracheobronchial tree. This helps to prevent postoperative pneumonitis and shunting, the end result of which may be a requirement for mechanical ventilation, which is an extremely hazardous procedure for a patient with a recently completed tracheal reconstruction. During the operation, the assistant must be vigilant in the clearance of blood and secretions by careful suctioning and must not allow them entry into the airway (even in the presence of an inflated cuff). Postoperatively, the patient is instructed to maintain airway clearance with gentle coughing and other chest physical therapy maneuvers. If these techniques are inadequate, gentle tracheal suctioning is performed. If all of these maneuvers prove unsuccessful, then the flexible bronchoscope is used to clear secretions.

Palliation and the Use of Airway Stents

Patients presenting with advanced unresectable cancers or with locoregional recurrence and airway compromise represent a unique challenge both clinically and ethically. Expandable airway stents can relieve airway obstruction, providing an opportunity for patients to recover from interventions and be actively involved in treatment or palliative decision making. Expandable stents can however be problematic with issues including migration, perforation, and retained secretions in up to 15% of patients.[23] There is little compelling evidence that stents dramatically extend the lives of patients, but they do provide an opportunity to address the issue of acute airway compromise and have an important role in the management of patients with primary or recurrent tracheal tumors.

Outcomes

Treatment-related outcomes for cervical tracheal cancers are dependent on histology, stage of presentation, and resectability. Urdaneta et al.[24] published a SEER review of patients registered between 1973 and 2004 identifying 578 patients with primary tracheal tumors. For the entire dataset, overall survival at 5 years was 27.1%. The overall survival for patients with localized cancer was 46.8% at 5 years and for patients with regional metastasis 25.5% at 5 years. In this series, nodal involvement regardless of histology was associated with a 10.4% 5-year survival. Patients with a primary histologic diagnosis of SCC had a 5-year survival of 12.6%. Patients with a diagnosis of adenoid cystic carcinoma had a 5-year survival of 74.3%, reflecting the more indolent and longer survivals seen in this subset of patients.

The largest single institution series has been reported from the Massachusetts General Hospital with 191 patients treated for primary tracheal tumors between 1962 and 2002.[7] These authors report a series of 90 SCCs with 5- and 10-year survivals of 39% and 18%, respectively. In the same publication, they report a series of 101 adenoid cystic carcinomas with 5- and 10-year survivals of 52% and 29%.

Other series from large institutions include the series from MD Anderson with 5- and 10-year survivals of 20% and 10% for SCC and 5- and 10-year survivals of 45% and 28% for adenoid cystic carcinoma.[18]

Two European series have reported outcomes with adenoid cystic carcinoma with 5- and 10-year survivals of 73% and 57%, respectively, in

one series from France and 77% and 41% at 5 and 10 years from a center in Holland.[9,17]

Novel Reconstructive Approaches

The current standard for reconstruction of cervical tracheal resection is primary end-to-end anastomosis either trachea to trachea or cricotracheal repair. A number of centers have attempted tracheal reconstruction using nontraditional techniques particularly where primary repair is not feasible. The majority of these patients have been previously treated with radiotherapy or have low-grade tumors with a good prognosis such as papillary carcinoma of the thyroid or chondrosarcoma of the trachea or cricoid. A number of centers have reported the use of cutaneous free flaps with either intraluminal or extraluminal stenting.[25] Conceptually, this would seem an appropriate option; however, even when these flaps are thin, they will not maintain a rigid structure. More problematic however is the presence of skin in the upper airway. Long segments of skin lead to airway crusting and an inability to clear secretions from the lower airway as a result of the absence of a ciliated lubricated mucosal surface.

Other authors have considered and used the creation of constructs incorporating vascularized carriers usually fascial free flaps incorporating cartilage or bone with mucosal grafts (Fig. 17.5A–C). These have been used for partial tracheal defects with some success.[26]

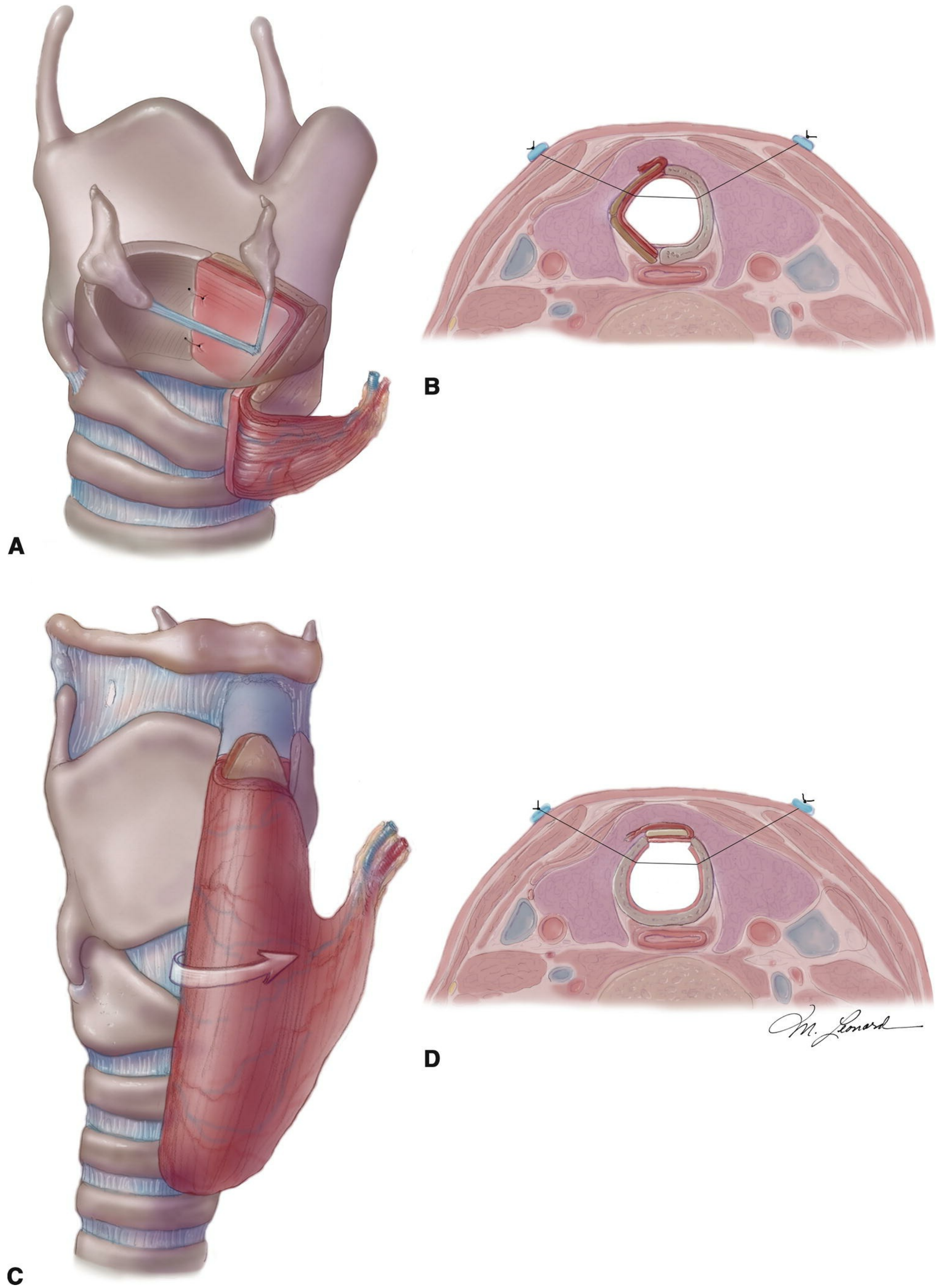
A
B
C
D
M. Leonard

Figure 17.5. A and B: Vascularized composite allograft concept, concept for cricoid and upper tracheal reconstruction of partial cricoid or tracheal defects. **C and D:** Concept for reconstruction of central tracheal defect or stenosis.

Delaere and his group have used decellularized allografts vascularized by placing them in the forearm site. Once vascularized, they introduce recipient mucosal grafts from the nasal mucosa to recreate the luminal epithelium and then transfer the construct as a partial tracheal transplant vascularized through the radial artery and its venae commitantes.[27,28] This technique requires a number of months to create the construct and requires short-term immunosuppression as the allograft is introduced to the arm. This technique clearly has no application in high-grade cancer of the trachea but has been used in low-grade tumors with success.

Macchiarini and colleagues[29] have attempted a number of allograft tracheal transplants. In this approach restricted to patients with stenosis and congenital deformities, a decellularized allograft is recellularized in a bioreactor with autologous stem cells to recreate the supported structure and epithelial components. This technique is interesting but currently has no role in the management of malignant tracheal tumors. Early reports have demonstrated the need for continuous stenting putting in question the success and probability of long-term success with this technique of airway reconstruction.

SUMMARY

Primary cancers of the cervical trachea are extremely rare, with many patients presenting with late-stage disease. Two types of histology predominate, SCC and adenoid cystic carcinoma, each with quite different natural clinical courses. Airway management at presentation can be extremely challenging even to the most experienced airway surgeon and require an experienced team including anesthesia. Primary treatment for malignant tumors is multimodal with surgery and adjuvant radiotherapy or chemoradiation advocated for the majority of resectable patients. Primary nonsurgical therapy is reserved for patients with unresectable lesions. Surgical resection is best performed by teams with significant volume expertise in airway surgery.

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18 Cancer of the Neck

Jesus E. Medina

Cervical lymph node metastases in patients with squamous cell carcinoma of the upper aerodigestive tract have important prognostic significance; when they are present, survival decreases by ~50%.[1] Detection of lymph node metastases at an early stage, preferably when they are microscopic, is paramount because the prognosis worsens as the extent of the metastases in the neck nodes (N stage) increases[2] (Fig. **18.1**). Depending on the location and stage of the primary tumor and the cervical lymph nodes, management of the neck may require surgery, radiation therapy, or both, and in some instances, it may also require chemotherapy. I begin this chapter presenting basic concepts such as surgical anatomy, staging, and nomenclature, and then, will outline the principles of management of the clinically negative (N0) and positive (N1/N3) neck.

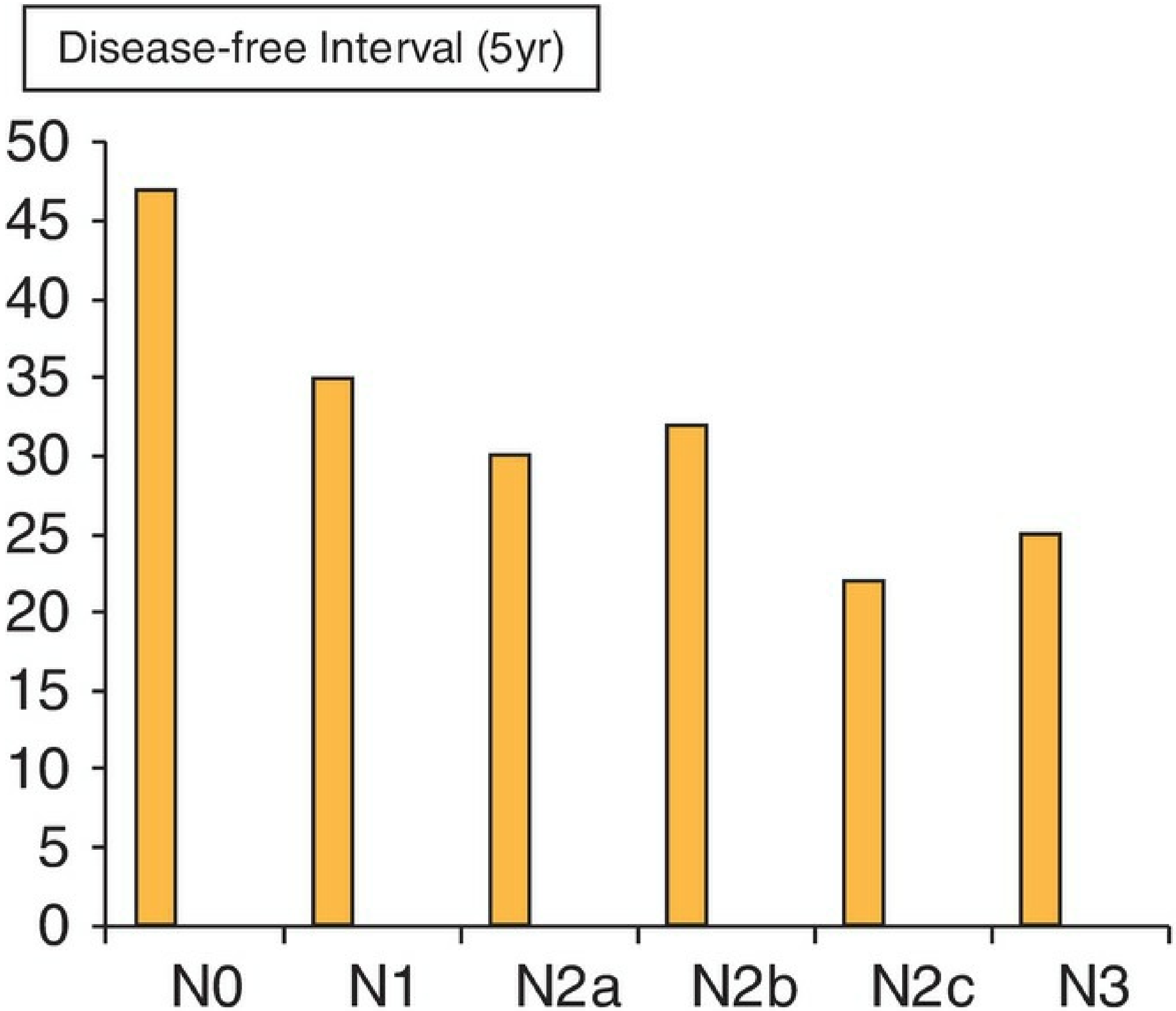

Figure 18.1. Impact of the extent of neck metastases (N stage) on prognosis. Disease-free interval according to TNM staging.

(Modified from Kowalski LP, Bagietto R Lara JR, et al. Prognostic significance of the distribution of neck node metastasis from oral carcinoma. *Head Neck.* 2000;22:207–214.)

ANATOMY

A neck dissection is the mainstay of the surgical treatment of many patients with cancer of the head and neck. A thorough knowledge of the anatomy of the neck is necessary to perform a neck dissection well. Such a discussion of the anatomy of the neck is not within the scope of this chapter. However, it is appropriate to highlight the pertinent surgical anatomy of certain structures that are particularly relevant, in the course of performing neck dissections.

Marginal Mandibular Branch of the Facial Nerve

The inferior division of the facial nerve divides into cervical and marginal branches, a short but variable distance behind the anterior border of the lower portion of the parotid gland (Fig. 18.2). The "lower" cervical branch runs downward and forward and, after exiting the parotid, is located between the anterior border of the parotid and the submandibular gland; it "terminates" in the platysma muscle, a variable distance below the submandibular gland. The marginal branch subdivides further, at about the level of the angle of the mandible, into an "upper" cervical branch and the marginal branch. The upper cervical branch overlies the posterior and then the inferior portions of the submandibular gland, as it curves upward to enter the platysma about 1.5 to 2 cm below the inferior border of the mandible. It is usually not possible to preserve the cervical branches of the facial nerve when performing a neck dissection that includes the submandibular triangle (level I). However, it is often possible to preserve these branches when performing a submandibular gland excision.

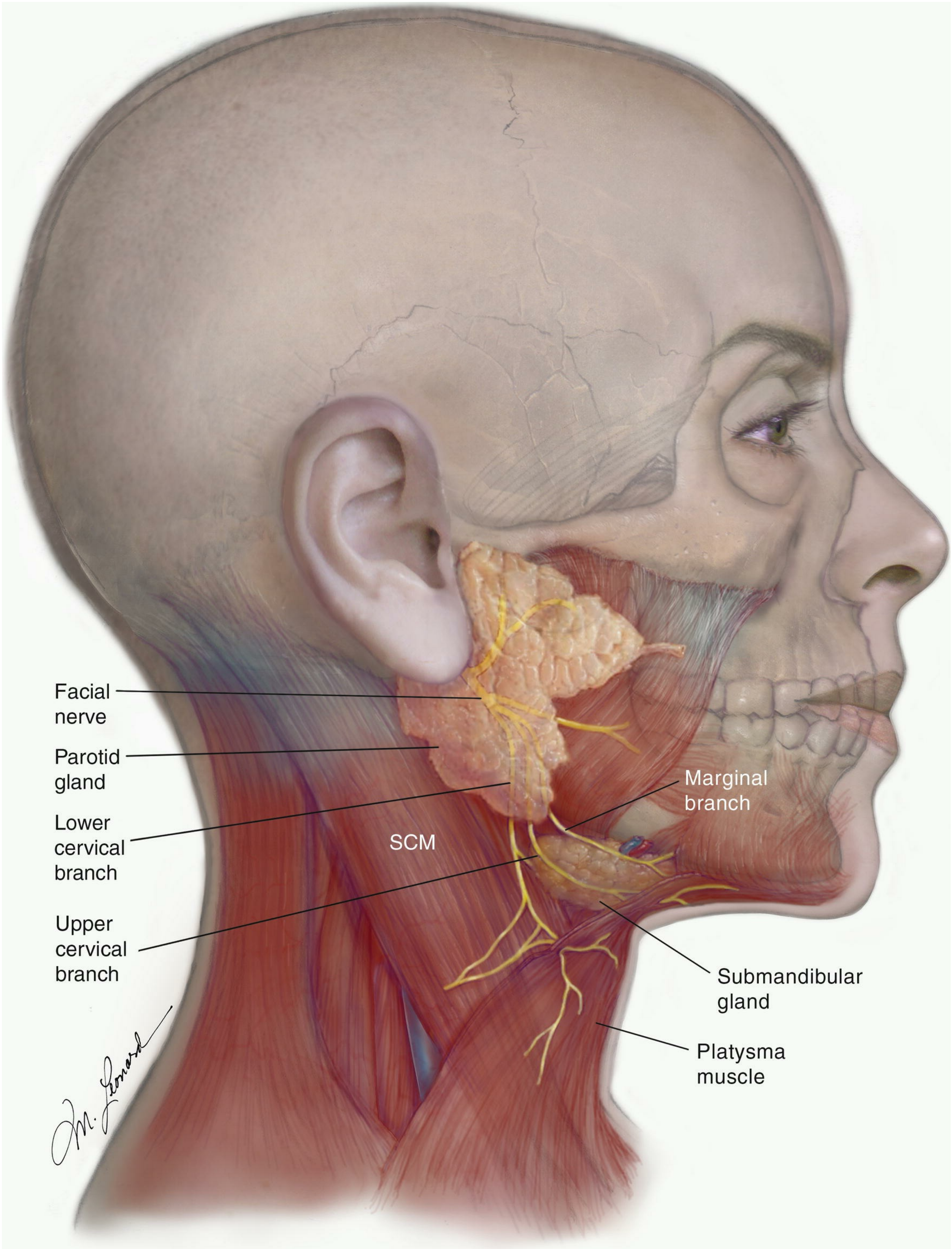

Figure 18.2. Anatomy of the inferior division of the facial nerve: 1. Marginal

mandibular branch; 2. Upper cervical branch; 3. Lower cervical branch.

The marginal branch runs forward, in a slightly oblique, upward direction; it is located deep to the superficial cervical fascia, between the inferior border of the mandible and the superior border of the submandibular gland. When performing a neck dissection, this nerve is usually identified about 1 cm in front of and inferior to the angle of the mandible by incising the superficial layer of the deep cervical fascia that envelops the submandibular gland, immediately above the gland, in a direction parallel to the direction of the nerve. The incised fascia then is gently pushed superiorly, exposing the nerve that lies deep to it but superficial to the adventitia of the anterior facial vein. The submandibular retrovascular lymph nodes are usually in close proximity and medial to the nerve and must be carefully dissected away from it. As this is done, the facial vessels are exposed and can be divided.

Identifying the marginal mandibular branch is essential in performing an adequate excision of the lymph nodes in the submandibular triangle. The practice of ligating the anterior facial vein low in the submandibular triangle and retracting it superiorly to “protect the marginal branch” can also result in elevation of the prevascular and retrovascular lymph nodes, thus precluding their appropriate removal. When indicated, it is preferable to identify the nerve and thoroughly remove these lymph nodes.

Spinal Accessory Nerve

The spinal accessory nerve (SAN) is located medial to the digastric and stylohyoid muscles and lateral or immediately posterior to the internal jugular vein (IJV) (Fig. 18.3). Occasionally, the superior portion of the nerve is posterior–medial to the vein. The nerve then runs obliquely inferior and backward to reach the medial surface of the sternocleidomastoid muscle (SCM) near the junction of its superior and middle thirds (two to three fingerbreadths below the mastoiditis). Although the nerve can continue its downward course entirely medial to the muscle (18%), more commonly, it traverses and appears in the posterior border (82%).[3] Here, the nerve is always located above the point where the greater auricular nerve turns around the posterior border of the SCM, also known as Erb point (Fig. 18.4).[4] The mean distance between the Erb point and the SAN is 10.7 mm, SD ± 6.3. It

then runs through the posterior triangle of the neck and crosses the anterior border of the trapezius muscle. The mean distance between this point and the clavicle is 51.3 mm, SD ± 17.[4] Two anatomic characteristics of this portion of the nerve are relevant to avoid injuring it in the course of a neck dissection. First, the SAN is located rather superficially as it courses through the middle and low posterior triangle of the neck, and it can be easily injured while elevating the skin flaps in the posterior neck. Second, the nerve does not enter the trapezius muscle at the anterior border of it but courses along the deep surface of the muscle in close relationship with the transverse cervical vessels. Therefore, isolating the nerve to the level of the anterior border of the trapezius does not ensure its preservation during surgical dissection below this point, particularly in a bloody operative field.

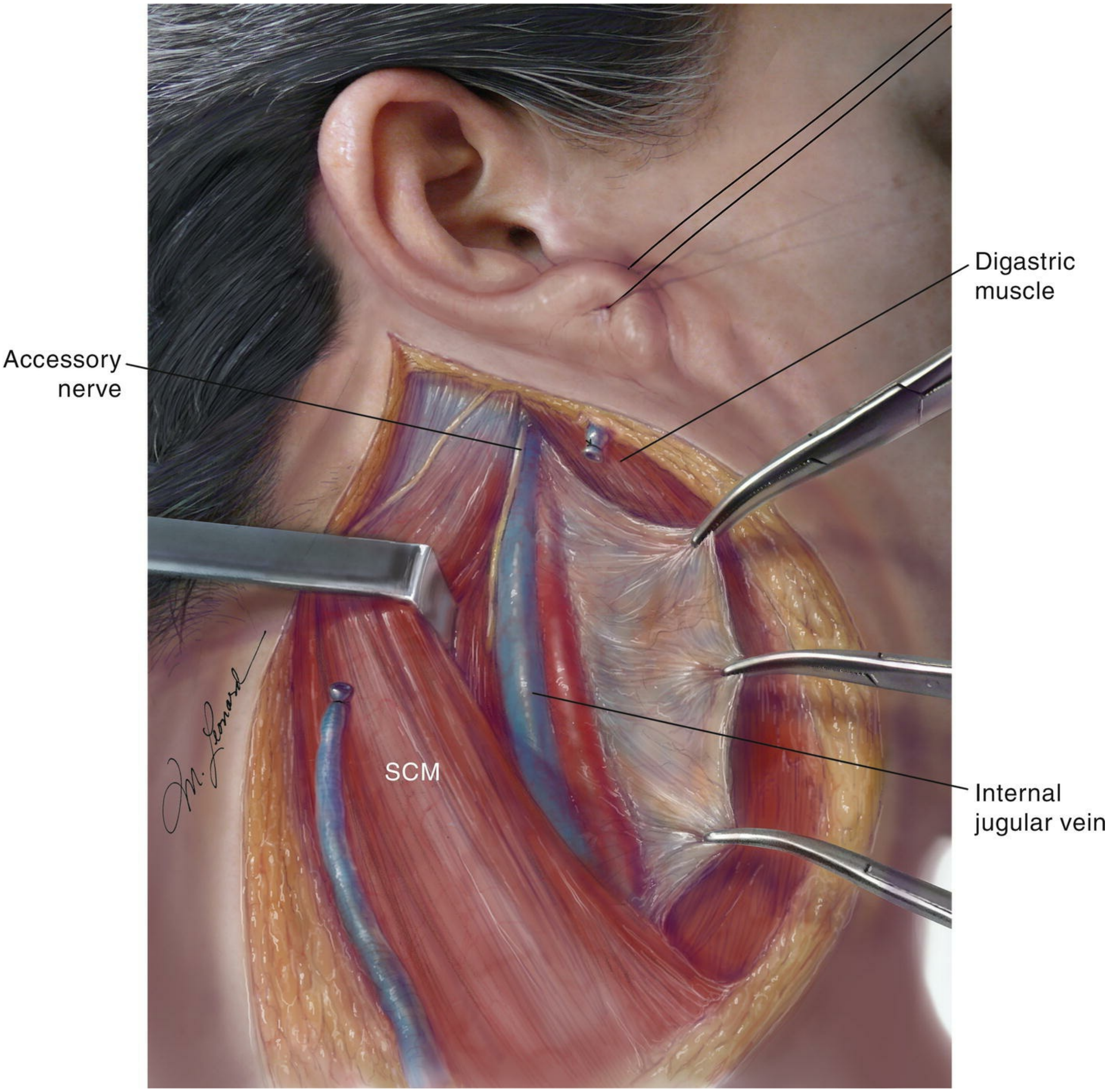

Figure 18.3. The SAN in its most common position in the superior aspect of the right neck: lateral and slightly posterior to the IJV.

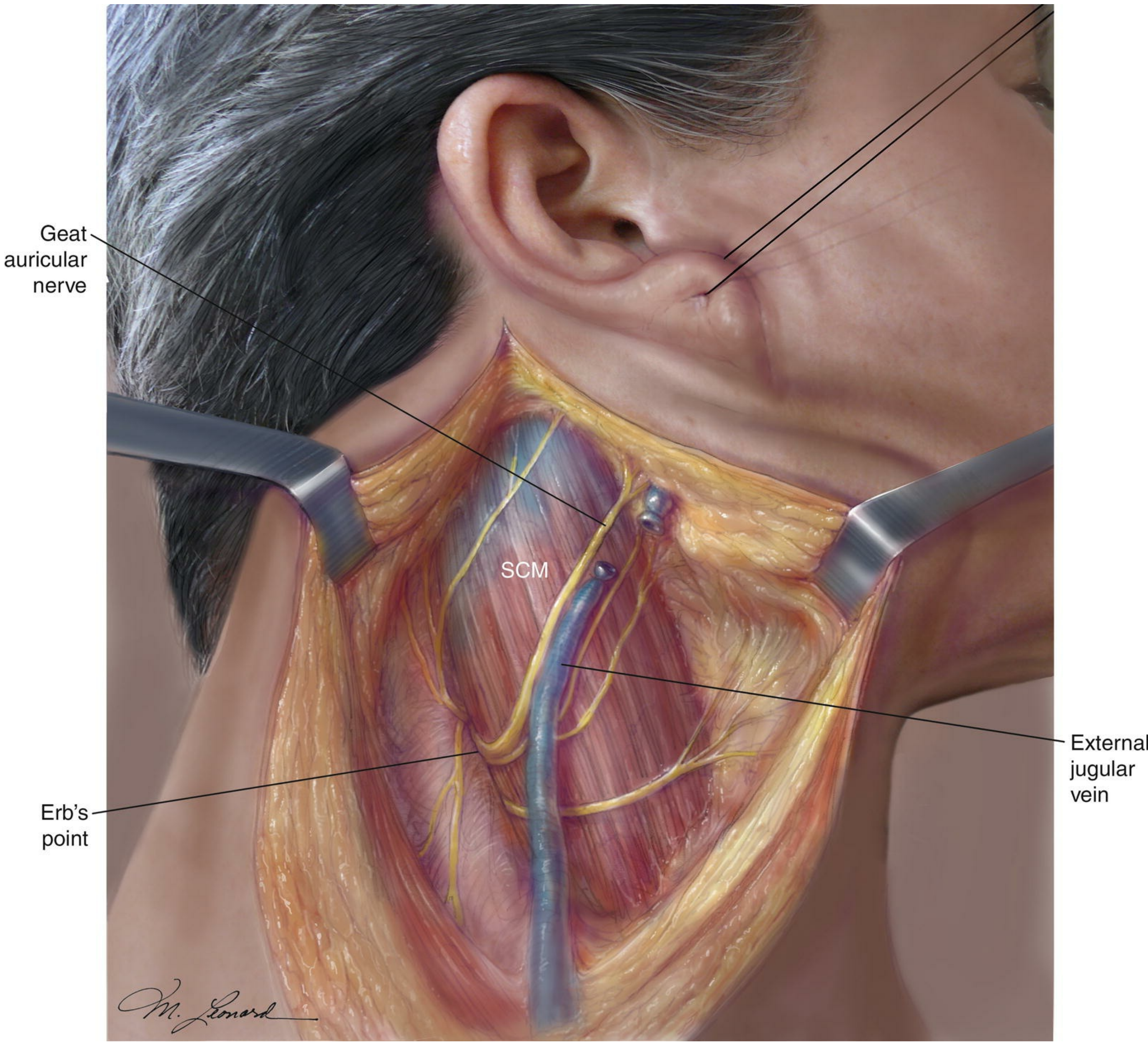

Figure 18.4. The spinal accessory in the posterior triangle of the neck. 1. Erb point; 2. The SAN is usually located about 1 cm above Erb point.

A common sequela in patients who undergo neck dissection is related to the removal of the SAN or to dysfunction of this nerve subsequent to its dissection during surgery. The resulting paralysis or paresis of the trapezius muscle, one of the most important shoulder abductors, causes destabilization of the scapula with progressive flaring of it at the vertebral border, drooping, and lateral and anterior rotation. The loss of the trapezius function decreases the patient's ability to abduct the shoulder above 90 degrees at the shoulder. Paralysis of the trapezius muscle causes a clinical syndrome characterized by weakness and deformity of the shoulder girdle, usually accompanied by

pain.[5] The shoulder pain appears to be secondary to increased supportive demands on and strain of the levator scapulae and rhomboid muscles. Furthermore, adhesive capsulitis of the glenohumeral capsule may result in a “frozen shoulder” leading to a chronic disability and impaired quality of life.[6]

Preservation of the SAN to avoid this cumbersome sequela has been one of the reasons for the development of the modified radical and selective neck dissections (SNDs) that are commonly used today. Interestingly, varying degrees of shoulder dysfunction can occur, even when the SAN is preserved during a neck dissection. Therefore, it is important for the surgeon to understand the anatomy of the SAN and the importance of early diagnosis and rehabilitation when dysfunction occurs.

Nerve to the Levator Scapulae Muscle

The levator scapulae is a triangular muscle located deep in the lateral aspect of the neck, anterior and medial to the splenius capitis muscle. It extends from the transverse process of the atlas and the next three cervical vertebrae to the superior angle and the spine of the scapula. The action of the levator scapulae is to raise the medial angle of the scapula and incline the neck to the corresponding side with rotation of the neck in the same direction. With the trapezius muscle, the levator scapula makes a shoulder shrug possible. Because one of the functions of the levator is to draw the scapula and the shoulder upward and medially, inadvertent or unnecessary resection of the nerves to it during a neck dissection, particularly a radical neck dissection (RND), may accentuate the resulting deformity and functional disability of the shoulder.

The nerves to the levator scapulae, which vary in number from 1 to 3, branch off the 4th and 5th cervical nerves and travel posteriorly and inferiorly. They cross the anterior border of the levator scapulae and remain on the surface of the muscle for a short distance. The nerves to the levator scapulae are deep to the fascia of this muscle; thus, in the course of any neck dissection, but especially in an RND or an modified radical neck dissection (MRND), it is crucial to keep the plane of dissection superficial to the fascia of the levator in order to preserve these nerves. The dorsal scapular nerve is inconsistent in its anatomic relations in the posterior triangle of the neck and contributes to the innervation of the levator scapulae in a minority of cases.[7]

Thoracic Duct

Inadvertent puncture or transection of the thoracic duct at the base of the neck can result in a chylous fistula, a relatively infrequent but potentially cumbersome complication of a neck dissection. Knowledge of the usual location and course of the thoracic duct is paramount whenever a dissection involves the supraclavicular, lower jugular (level IV) region. It is, perhaps, even more important when the surgeon is called on to search for and repair a chyle fistula during or after a neck dissection.

The thoracic duct is located medial to and behind the common carotid artery and the vagus nerve (Fig. 18.5). From here, it arches upward, forward, and laterally, passing behind the IJV and in front of the anterior scalene muscle and the phrenic nerve. It then opens into the IJV, the subclavian vein, or near the angle formed by the junction of these two vessels. The duct is anterior and medial to the thyrocervical trunk and the transverse cervical artery. To prevent a chyle leak, the surgeon also must remember that the thoracic duct may be multiple in its superior aspect and that at the base of the neck it usually receives a jugular, a subclavian, and other minor lymphatic trunks, which must be ligated or clipped individually.

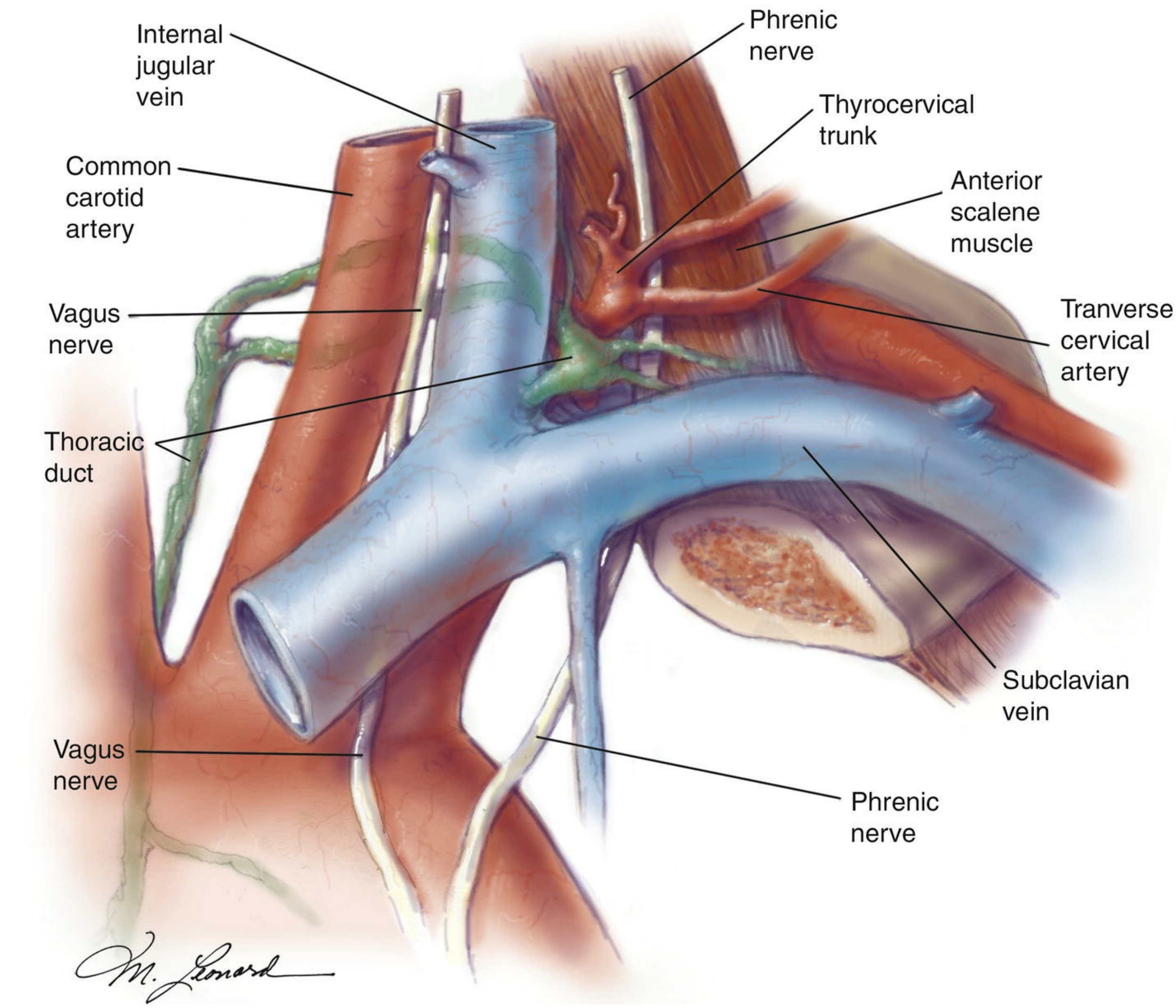

Figure 18.5. Anatomic relations of the thoracic duct. 1. Vagus nerve; 2. Common carotid artery; 3. Internal jugular vein; 4. Phrenic nerve; 5. Thoracic duct draining into the subclavian vein; 6. Transverse cervical artery.

Lymph Nodes of the Neck

The lymph node regions of the neck are shown in Figure 18.6. The six levels currently used encompass the complete topographic anatomy of the neck. The concept of sublevels has been introduced into the classification because certain zones have been identified within the six levels, which may have clinical significance.

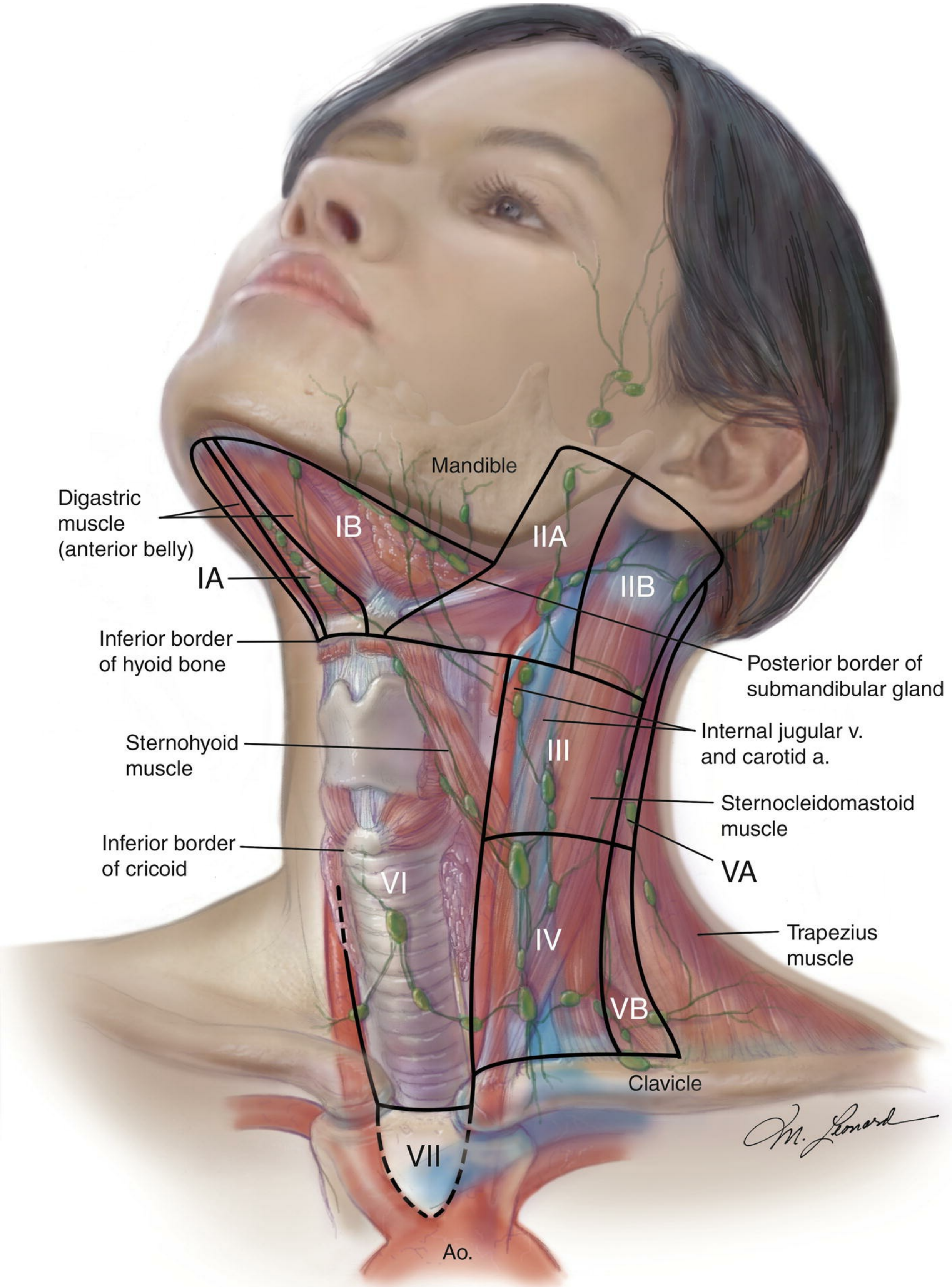
Mandible
Digastric muscle (anterior belly)
IA
IB
IIA
IIB
Inferior border of hyoid bone
Posterior border of submandibular gland
Internal jugular v. and carotid a.
Sternohyoid muscle
III
Sternocleidomastoid muscle
Inferior border of cricoid
VI
VA
IV
Trapezius muscle
VB
Clavicle
VII
Ao.
M. Leonard

Figure 18.6. The lymph node regions/“levels” of the neck.

Level I is divided into two sublevels. Sublevel IA (submental) includes the lymph nodes within the inferiorly based triangle bound by the anterior belly of the digastric muscles and the hyoid bone. Sublevel IB (submandibular) includes the lymph nodes within the boundaries of the anterior belly of the digastric muscle, the stylohyoid muscle, and the inferior border of the body of the mandible.

Level II (upper deep jugular) includes the lymph nodes located around the upper third of the IJV and adjacent SAN extending from the level of the skull base to the level of the inferior border of the hyoid bone. The anterior/medial boundary is the stylohyoid muscle (the radiologic correlate is the vertical plane defined by the posterior surface of the submandibular gland), and the posterior (lateral) boundary is the posterior border of the SCM. Two sublevels are recognized in level II: sublevel IIA, nodes located anterior/medial to the vertical plane defined by the SAN, and sublevel IIB, nodes located posterior/lateral to the vertical plane defined by the SAN.

Level III (mid deep jugular) includes the lymph nodes located around the middle third of the IJV extending from the inferior border of the hyoid bone to the inferior border of the cricoid cartilage. The anterior/medial boundary is the lateral border of the sternohyoid muscle, and the posterior/lateral boundary is the posterior border of the SCM.

Level IV (lower deep jugular) encompasses the lymph nodes located around the lower third of the IJV extending from the inferior border of the cricoid cartilage to the clavicle.

The anatomic boundary that separates the medial border of levels III and IV from the lateral border of level VI has traditionally been the lateral border of the sternohyoid muscle, a landmark that cannot be easily discerned on imaging studies. Therefore, the medial aspect of the common carotid artery has been suggested as an alternate boundary to separate these levels in an axial plane in imaging studies.[8]

Level V (posterior triangle) comprised predominantly of the lymph nodes located along the inferior half of the SAN and the transverse cervical artery. The supraclavicular nodes are also included in the posterior triangle group. The superior boundary is the apex formed by convergence of the

sternocleidomastoid and trapezius muscles, the inferior boundary is the clavicle, the anterior boundary is the posterior border of the SCM, and the posterior boundary is the anterior border of the trapezius muscle. A horizontal plane marking the inferior border of the anterior cricoid arch separates two sublevels. Sublevel VA, above this plane, includes the spinal accessory nodes. Sublevel VB, below this plane, includes the nodes that follow the transverse cervical vessels and the supraclavicular nodes with the exception of Virchow node, which is located in level IV.

Level VI (anterior compartment) lymph nodes in this compartment include the pre- and paratracheal nodes, precricoid (Delphian) node, and the perithyroidal nodes including the lymph nodes along the recurrent laryngeal nerves. The superior boundary is the hyoid bone, the inferior boundary is the suprasternal notch, and the lateral boundaries are the common carotid arteries.

Level VII refers to the extension of the paratracheal nodes below the suprasternal notch (the dividing line between levels VI and VII) to the level of the innominate artery.

Other Lymph Node Groups

Lymph nodes involving regions not located within these levels should be referred to by the name of their specific nodal group; examples of these are the superior mediastinal, the retropharyngeal, the periparotid, the buccinator, the postauricular, and the suboccipital lymph nodes.

The retropharyngeal lymph nodes (RPLNs) lie within a pad of adipose tissue located behind the posterior wall of the pharynx and anterior to the prevertebral fascia and the cervical sympathetic trunk and ganglion. This pad of adipose tissue extends from about the level of the carotid bifurcation to just inferior to the skull base. The RPLN are divided into medial and lateral groups; the medial group of nodes lies behind the pharyngeal midline at a level between the first and fourth cervical vertebrae. The lateral group of nodes, better known as the nodes of Rouviere, are contained within a sliver of adipose tissue located immediately medial to the internal carotid artery. The RPLN receive lymphatic drainage from the nasopharynx, tonsil fossa, the walls of the oropharynx and the hypopharynx, and the posterior ethmoid sinuses.

STAGING

After completing the clinical evaluation of a patient with squamous cell carcinoma of the head and neck region, the disease should be classified according to stage. The staging for the lymph nodes proposed by the American Joint Committee on Cancer in 2009[9] is outlined below:

NX: Regional lymph nodes cannot be assessed.

N0: No regional lymph node metastasis.

N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension.

N2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N2a: Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension.

N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension.

N2c: Metastasis in bilateral or contralateral nodes no more than 6 cm in greatest dimension.

N3: Metastasis in a lymph node more than 6 cm in greatest dimension.

Staging of the neck in patients with carcinoma of the nasopharynx is different because the distribution and the prognostic impact of regional lymph node metastasis from cancer of the nasopharynx, particularly of the undifferentiated type, are different from that of other cancers of the head and neck mucosa and justifies the use of the following scheme:

NX: Regional lymph nodes cannot be assessed.

N0: No regional lymph node metastasis.

N1: Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa.

N2: Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa.

N3: Metastasis in a lymph node(s) >6 cm and/or to supraclavicular fossa.

N3a: Greater than 6 cm in dimension.

N3b: Extension to the supraclavicular fossa.

CLASSIFICATION OF NECK DISSECTIONS

Several cervical lymph node dissections are currently used for the surgical treatment of the neck in patients with cancer of the head and neck region. To standardize the nomenclature used to refer to these operations, it is essential to adopt a common nomenclature for the groups of lymph nodes in the neck, such as the one outlined above. The current classification of neck dissections recommended by the American Academy of Otolaryngology: Head and Neck Surgery (Table 18.1) takes into account the groups of lymph nodes of the neck that are removed and secondarily the anatomic structures that may be preserved, such as the SAN and the IJV. Analyzing neck dissections from these two points of view, there are essentially four anatomic types of neck dissections: radical, modified radical, selective, and extended. Recently, clinicians from around the world have proposed a nomenclature for neck dissection, which, if recognized internationally, would be "logical, unambiguous, precise, and easy to remember."[10]

Table 18.1 Classification of Neck Dissections

2001 Classification	2010 Proposed Classification
1. Radical neck dissection	1. ND (I–V, SCM, IJV, CNXI)
2. Modified radical neck dissection	2. ND (I–V, SCM, IJV), ND (I–V, IJV, CNXI), ND (I–V)
3. Selective neck dissection (SND): SND (I–III/IV) SND (II–IV) SND (II–V, postauricular, suboccipital) SND (level VI)	3. ND (I, II, II/IV) ND (II, III, IV) ND (II, III, IV,V, postauricular, suboccipital) ND (VI)
4. Extended neck dissection	4. ND (levels removed, nodes or structures removed)

In this classification, the following three descriptors are used to label a neck dissection:

1. “ND” to represent neck dissection, which is prefaced by either “L” or “R” for side. If bilateral, both sides must be classified independently.
2. The levels and sublevels of lymph nodes removed designated by Roman numerals I through VII in ascending order. For levels that contain sublevels (I, II, and V), listing of the level without a sublevel indicates that the entire level (both A and B) was excised.
3. The nonlymphatic structures removed designated by their internationally recognized initials, that is, SCM for sternocleidomastoid muscle and IJV for internal jugular vein.

The advantage of this classification is that it conveys precisely the groups of lymph nodes included as well as the nonlymphatic structures removed in a neck dissection. This will allow a standardized reporting and meaningful comparison of outcomes.

Irrespective of the nomenclature used, it is the responsibility of the surgeon to divide or otherwise orient the neck dissection specimen identifying the different groups of lymph nodes it contains. Only then can the

pathologist render a report that is useful clinically and prognostically. Such a report describes the location and number of lymph nodes examined, the number of nodes that contain cancer, and the presence or absence of extra capsular extension of tumor.

MANAGEMENT OF THE N0 NECK

The initial management of the clinically N0 neck is dictated by the treatment modality that is ideal or is selected for the management of the primary cancer. Therefore, we will discuss the management of the N0 neck when the primary cancer is treated initially with surgery and when it is treated initially with radiation alone or in combination with chemotherapy.

Primary Cancer Treated with Surgery

Most primary squamous cell carcinomas of the oral cavity are treated with surgery. Selected carcinomas of the oropharynx and larynx are increasingly treated with transoral laser excision or robot-assisted surgery. Removing the lymph nodes, that is, performing a neck dissection in every patient with these tumors, is obviously impractical, because not everyone of them would have metastases in the lymph nodes. Ideally, dissection of the lymph nodes would be limited to those patients that are most likely to have metastases. Unfortunately, detection of "subclinical," microscopic metastases in the lymph nodes of the neck in patients without palpable adenopathy (clinically N0) remains a challenge to the clinician.

Clinical Examination

Examination of the neck by palpation is not uniformly reliable. It is commonly accepted that the reported error rate in assessing the presence or absence of cervical lymph node metastases by palpation ranges from 20% to 50%. The factors responsible for this variation are not only the ability and experience of the examiner but also the patient's habitus and previous treatment to the neck with surgery or radiation therapy.

In the quest for a way to identify those patients who harbor "subclinical metastases" in the lymph nodes, clinicians have used a variety of resources spanning from noninvasive methods such as ultrasonography (US) to more

invasive procedures such as sentinel lymph node biopsy (SLNB). However, the decision to recommend elective dissection of the neck is currently based mainly on the probability of lymph node metastases, which is determined on the basis of the location and stage of the primary cancer and several other cancer and patient-related parameters.

Ultrasonography, Computed Tomography, and Magnetic Resonance Imaging

These imaging modalities have a higher sensitivity and specificity than clinical examination in the detection of metastases in lymph nodes. In a prospective study of 48 patients who were to undergo neck dissection, Haberal et al. found that the sensitivity and specificity of palpation for the detection of metastases in the lymph nodes were 64% and 85%, respectively, whereas the corresponding values for US were 72% and 96% and for computed tomography (CT) 81% and 96%.[11] Adams et al.[12] reported similar results for US and CT; in addition, they reported a sensitivity of 80% and a specificity of 79% for magnetic resonance imaging (MRI). However, these imaging modalities failed to detect metastases, in this and other studies, in 19% to 28% of the patients staged clinically N0; thus, a "negative" US, CT, or MRI of the neck cannot be relied upon enough to withhold elective treatment of the cervical lymph nodes.

There are several reasons for the poor performance of current imaging studies in the detection of occult metastases in lymph nodes. First, size is the imaging criterion used most often to consider a cervical node suspicious for metastasis; nodes located in levels I and II larger than 1.5 cm in maximum diameter and nodes larger than 1 cm in other regions of the neck are considered suspicious.[13] Although a correlation exists between the size of a lymph node and the presence of histologic metastasis, not all enlarged lymph nodes contain metastatic deposits, and nodes smaller than 1 or 1.5 cm can contain metastases (Table 18.2). In fact, 33% of all metastases from squamous cell carcinomas of the head and neck are found in lymph nodes smaller than 1 cm.[14,15] Second, 10% of cancer-positive neck dissection specimens contain only metastases <3 mm in diameter, and more importantly, 25% of all clinically occult lymph node metastases are too small to be detected by any of the currently available imaging techniques.[14]

Table 18.2 Nodal Size and Presence of Histologic Metastases

Node Size (cm)	Histologic Status (%)		
	Negative	Positive	Positive with Extranodal Extension
1	67	33	14
2	38	62	26
3	19	81	49
4	12	88	71
5	0	100	76

From Mozzillo N, Chiesa F, Botti G, et al. Sentinel node biopsy in head and neck cancer. *Ann Surg Oncol.* 2001;8(suppl):105S, with permission.

Positron Emission Tomography

Prospective studies using 18-fluorodeoxyglucose positron emission tomography (PET) to assess lymph node metastases from squamous cell carcinomas of the oral cavity have shown a sensitivity and specificity higher than MRI, CT, and US. However, current FDG PET techniques are also limited in the detection of tumor foci smaller than 1 cm.[16–18]

Kyzas et al.[19] performed a meta-analysis of 32 studies that assessed the diagnostic performance of PET scans in patients with squamous cell carcinoma of the head and neck. In patients staged clinically N0, the sensitivity of 18FDG PET scan was only 50% (95% CI = 37% to 63%), whereas the specificity was 87% (95% CI = 76% to 93%). These authors also compared the performance of PET scan with that of “conventional diagnostic methods,” that is, CT, magnetic resonance imaging, and ultrasound with fine needle aspiration by analyzing studies that had used all these diagnostic methods on the same patients. The sensitivity and specificity of PET scan was 80% and 86%, respectively, whereas for the “conventional diagnostic tests,” they were 75% and 79%.

Ng et al.[20] showed that the visual correlation of 18FDG PET with contrast-enhanced CT/MRI was more accurate than 18FDG PET alone for the detection of subclinical lymph node metastases. In 134 patients with squamous cell carcinoma of the oral cavity who were staged N0 clinically, they found a sensitivity of 51.4% for 18FDG PET, which increased to 57.1% after visual correlation with CT or MRI. This increment stemmed from the correction of false-negative 18F-FDG PET results caused by necrotic nodes. Ozer et al.[21] reported a sensitivity of 57% and specificity of 82% for the detection of occult metastasis by 18F-FDG PET/CT in 112 patients with clinically negative necks on physical examination, CT, and/or MRI.

Liao et al.[22] recently reported a meta-analysis comparing CT, MRI, PET, and ultrasound for the detection of cervical lymph node metastasis in patients with clinically N0 necks. They found no significant differences in sensitivity and specificity among these imaging modalities, with the exception that CT had a higher specificity than ultrasound.

Thus, at the present time, the role for PET scan in the evaluation of the N0 neck is limited as it will not detect subclinical metastases in 20% to 50% of the cases.

Ultrasound-Guided Fine-Needle Aspiration Biopsy

In an attempt to overcome the lack of sensitivity of morphologic imaging criteria, US was combined with US-guided fine needle aspiration cytology (US-FNAB). This technique appeared more promising for the preoperative evaluation of the N0 neck as it enabled sampling of lymph nodes as small as 3 mm in diameter and added the advantages of cytologic evaluation.[23] However, the usefulness of this technique is strongly dependent on the skill and time of the ultrasonographer and on the experience of the cytopathologist. Furthermore, the outcomes of a wait-and-see policy after negative US-FNAB have been disappointing. In a study of 92 patients with cancer of the oral cavity, staged T1 and T2, who were observed after a negative US-FNAB, metastases in neck nodes became apparent subsequently in 19 (21%).[24] In a more recent study, Wensing et al. found that palpation and US with or without US-FNAB missed occult lymph node metastases in 22% of the patients with oral cavity squamous cell carcinoma.[25] These figures are troubling because the incidence of lymph node metastases in

patients with such cancers, who are observed without any intervention to the neck, is about 25%.

Sentinel Lymph Node Biopsy

SLNB is feasible and useful as a staging procedure in patients with early cancer of the oral cavity and in particular for patients with cancer of the oral tongue. Proponents of this technique point out that it allows accurate histopathologic staging of the neck by examining the sentinel lymph node (SLN) with serial sectioning and immunohistochemistry, and it avoids unnecessary neck dissection and its possible complications.

The SLNB is based on the principle that cancers metastasize via lymphatics to regional lymph nodes in an orderly fashion, that this process is embolic in nature, and that the lymph node that first receives lymphatic drainage from the primary site can be identified and excised for histologic analysis.[26]

Early studies in patients with squamous cell carcinoma of the mucosal surfaces of the head and neck investigated the methodology and feasibility of SLNB.[26]–[29] In general, the primary cancer should be accessible to infiltration with a radioisotope-labeled colloid to perform a lymphoscintigraphy and a blue dye injection to aid in intraoperative localization of the sentinel node. These localizing methods have been shown to be complementary. In a multicenter study, Ross and associates investigated SLNB in 134 patients with squamous cell carcinoma of the oral cavity and oropharynx, staged T1/T2 N0.[27] Lymphoscintigraphy was performed preoperatively; blue dye and a gamma probe were used intraoperatively to aid in the identification of sentinel nodes. Sentinel nodes were identified in 93% of the cases. The number of sentinel nodes varied, but in a previous series of 48 patients studied by Ross et al.,[30] the mean number of sentinel nodes harvested was 2.4.

Subsequent studies have examined the utility of SLNB in patients with oral cavity or oropharyngeal cancers staged T1/T2 N0. The sensitivity of the procedure is 90% when the histopathology of the sentinel node is compared with that of the neck dissection specimen.[31] It results in histopathologic upstaging of the clinically N0 neck in 36% of the patients when the nodes are examined with routine hematoxylin and eosin staining; serial sectioning and

immunohistochemistry upstage an additional 8% of the cases.[27] The detection of micrometastases can be further enhanced by using highly specific tumor markers and molecular methods.[32,33]

Recently, Civantos et al. reported the results of a North American Multi-Institutional Prospective Study that evaluated the utility of SLNB in T1/T2 oral SCCs.[34] The study included 140 patients (68% oral tongue, 19% floor of the mouth) from 25 institutions who underwent SLNB and SND (levels I to IV). The negative predictive value (NPV) was 94% when the SLNs were examined with hematoxylin and eosin stains and 96% when they were examined with serial sectioning and immunocytochemistry.[34] The NPV among experienced surgeons was 100% versus 95% for less experienced ones. The SLN was the only positive node in 51% of the cases with a positive SLN. The false-negative rate was 9.8% overall. Interestingly, however, the false-negative rate was 10% in patients with cancer of the oral tongue, but was 25% in patients with cancer of the floor of the mouth. In the experience of the University of Miami,[35] the NPV of SLNB was 88.5% in patients with cancers of the FOM and 95.8% when these patients were excluded. Similarly, Ross et al. have reported that the identification of SLNB in patients with cancer of the floor of the mouth was lower (86%) than in patients with cancer in other locations (97%); the sensitivity of SLNB in cancer of the floor of the mouth was also lower (80%), compared with other tumor locations (100%).[28] It appears that lymphoscintigraphy in cancers of the floor of the mouth is not as helpful in identifying the SLN; this is most likely due to the "shine-through" effect of the radioactivity at the primary, which obscures the lymph nodes in level I, the primary echelons of lymphatic drainage for the floor of the mouth and inferior Alvestar ridge. Obviously, this limits the utility of SLNB in patients with tumors in these locations.

Probability of "Subclinical" Metastases

Because clinical examination and current imaging studies cannot reliably rule out the presence of metastases in patients clinically staged N0, therapeutic decisions in these patients are, for the most part, based on the probability of lymph node metastases for a given cancer. There is general agreement that elective treatment of the cervical lymph nodes is indicated when the risk of occult metastases exceeds 15% to 20%.[36] This probability varies with the site of the primary cancer, the stage of it (T stage), and other factors related to the

cancer, the patient, or both.

Carcinomas of the Oral Cavity

The probability of occult metastases derived from clinical and histopathologic data is outlined in Table 18.3.[41] Based on those figures, elective treatment of the neck is indicated in patients with T2, T3, and T4 cancers of the oral cavity, regardless of the subsite of origin. On the other hand, it is not necessary in patients with T1 cancer of the retromolar trigone. However, the probability of metastases is too variable to be dogmatic in cases with T1 cancers of other oral cavity subsites. Thus, there has been a search for other parameters that may be helpful in the decision making in these patients. Some investigators have proposed elaborate scoring systems based on several parameters,[42] but they have not proven practical. The thickness of the primary tumor has been shown to be variably useful in several studies and may be helpful in the decision making regarding elective treatment of the neck.[43,44] A meta-analysis of studies published before 2009 revealed that occult lymph node metastases are significantly more common when the thickness of the primary tumor is >4 mm. A practical advantage of using tumor thickness is that it can be evaluated with frozen section and the decision about neck dissection can be made intraoperatively.[45] Furthermore, recent reports indicate that high-resolution diagnostic intraoral US can be used in the determination of tumor thickness.[46] It should be pointed out, however, that in a recent study that evaluated multiple parameters potentially predictive of lymph node metastases in patients undergoing a thorough search for occult metastases by sentinel lymph node biopsy, tumor thickness failed to achieve statistical significance.[47]

Table 18.3 Oral Cavity Squamous Cell Carcinoma Incidence of Lymph Node Metastases by Stage

Site of Primary Tumor	Percentage of Necks with Node Metastases			
	T1	T2	T3	T4
Oral tongue[37]	18–38	30	57	76.5
Floor of the mouth	8.7–30	29	43.5	53.5
Retromolar trigone[38]	7–11	21	50	50–67.5
Buccal mucosa[39,40]	12–40	20–52	41–80	44–64

We recently conducted a systematic review of the literature dealing with tumor markers possibly associated with cervical metastasis in cancers of the oral tongue over the last 25 years.[48] Sixty-five articles met the inclusion criteria; of these, 51 papers provided adequate data for analysis. A total of 76 unique markers were reported. Adequate data was found for 61 of those markers. Thirteen markers were evaluated in two or more studies. Twenty-two markers had sensitivity >75%. Five markers achieved this in two or more studies; these were MMP-9 (0.80), VEGF (0.94), E-cadherin (0.90), cyclin D1 (0.85), and CD105 (0.82) with a combined sensitivity of 0.86. A total of 13 markers had specificity over 75%. p52 (0.86) and CD105 (0.94) achieved this in more than one study (combined specificity 0.90). Four markers had both sensitivity and specificity over 75%, namely, E-cadherin, CD105, VEGF, and osteopontin (0.87 and 0.97), respectively. Twenty-eight markers had a NPV > 75%. Four of them achieved this in two or more studies with a combined NPV of 0.91 (E-cadherin, VEGF, CD105, and cyclin D1). Two markers achieved an NPV >95%, namely, VEGF and osteopontin (combined NPV of 0.97). At the present time, we are studying five of these biomarkers (VEGF, E-cadherin, cyclin D1, CD105, osteopontin) in a cohort of patients with T1 and T2 cancers of the oral tongue with the purpose of building a predictive model for lymph node metastases.

Cancer of the Larynx

For glottic cancers, the frequency of nodal metastases is <8% for T1 and T2 tumors and varies between 11% and 16% for T3 and T4 tumors.[49–52] For

supraglottic cancers, the reported frequency of nodal metastases is higher, ranging from 14% to 42% for T1 and T2 tumors, 35% to 55% for T3, and 65% to 75% for T4 tumors.[10,53,54]

McGavran et al. found that the incidence of lymph node metastases was significantly higher in patients whose tumors measured more than 2 cm in diameter, were poorly differentiated, exhibited an infiltrating rather than a pushing margin, or exhibited perineural invasion. Unfortunately, these authors did not perform a multivariate analysis. More recently, Kowalski et al. performed a study of 103 patients with carcinoma of the larynx who underwent either unilateral or bilateral comprehensive neck dissection. A logistic regression analysis demonstrated that cancer site (supraglottic origin) and poor histologic differentiation were the only predictors of lymph node metastases. When they considered only cases staged N0, the probability of occult lymph node metastases was influenced significantly only by a supraglottic origin of the primary cancer.

Bilateral cervical lymph node metastases are present in about 6% of the patients with cancer of the larynx.[55] However, the frequency of bilateral metastases is higher in advanced supraglottic cancers that involve the midline and in patients with advanced unilateral/ipsilateral lymph node metastases.[25,56]

The possible predictive role of a number of other factors has been investigated. Mansour et al. studied 171 patients with cancers of the larynx and pharynx and found cervical metastases in 100% of tobacco users and in only 54% of nonusers ($p < 0.0001$). Extracapsular spread (ECS) was observed in 100% of tobacco users and 19% of nonusers ($p < 0.0001$). This study suggests that tobacco use is a possible risk factor for cervical metastasis and extracapsular spread in cancer of the larynx, and thus, it may be helpful information in planning therapy for patients with a clinically N0 neck.[26] In another study, carcinomas of the larynx with a depth of invasion ≥3.25 mm were associated with a rate of cervical lymph node metastasis significantly higher than cancers with a depth of invasion <3.25 mm ($p < 0.05$). Expression of epidermal growth factor (EGFR) is another potentially useful biologic marker. A significant correlation between expression of EGFR and the risk of lymph node metastases was observed by Maurizi et al.,[57] in a study of 140 cases of carcinoma of the larynx. In a similar study, Almadori et al.[58] observed that the 5-year lymph node metastasis-free survival was 66%

for patients with EGFR-negative larynx cancers compared with 15% for patients with EGFR-positive tumors.

Carcinoma of the Oropharynx

The oropharynx contains abundant lymphoid tissue (Waldeyer ring) and has a prominent network of lymphatics, which communicate freely across the midline. This explains the propensity of cancer of this region to metastasize to the regional lymph nodes, as well as the relatively high frequency of bilateral lymph node metastases (Table 18.4). The lymphatic drainage of the oropharynx occurs predominantly toward the upper and midjugular lymph nodes (levels II and III). The retropharyngeal nodes are a less common but important echelon in the lymphatic drainage of the oropharynx.

Table 18.4 Squamous Cell Carcinoma of the Oropharynx: Incidence of Lymph Node Metastases by Stage (Based on Histopathology of Neck Dissection Specimens)

	% of Patients with Lymph Node Metastases			
	T_1	T_2	T_3	T_4
Oropharynx	40%	55%	71%	69%

From Elsheikh MN, Ferlito A, Rinaldo A, et al. Do pathologic and molecular analyses of neck dissection specimens justify the preservation of level IV for laryngeal squamous carcinoma with clinically negative neck? *J Am Coll Surg.* 2006;202:320–323.

When cancer of the oropharynx is treated with surgery (open or transoral), based on the distribution of bilateral lymph node metastases shown in Table 18.5, a bilateral SND (levels II to IV) is indicated except for T1 and T2 cancers of the tonsil and well-lateralized T1 cancers of the base of the tongue and soft palate.

Table 18.5 Squamous Cell Carcinoma of the Oropharynx: Incidence of Bilateral Nodal Metastases[59]

Site of Primary Tumor	Percentage of Necks with Node Metastases				
	T1	T2	T3	T4	All T Stages
Tonsil	3.3	10.7	17.6	8.6	9.4
Base of the tongue	14.3	23.9	27	15.8	21.9
Pharyngeal walls	50	33.3	50	0	31.3
Soft palate	10	25	11	50	20

Treatment

Once it has been determined that the likelihood of metastases warrants elective dissection of the neck, the clinician faces the following decisions:

a. Whether to perform a neck dissection or to observe the neck and intervene only if and when lymph node metastases become apparent.
b. What type of neck dissection is appropriate.

Observation Versus Elective Neck Dissection

A prospective randomized study done in Brazil compared SND versus observation in a mixed cohort of patients with oral cavity cancers involving the tongue or floor of the mouth. This study, reported in 1994, showed significant benefit of elective neck dissection.[60] On the other hand, in the past 5 years, one prospective study and one retrospective study have shown that regional control of cancer and survival when the N0 neck is observed, and is dissected only if metastases develop subsequently, are comparable to those obtained with elective neck dissection. It should be noted that in the prospective study conducted by Yuen et al., 95% of the patients whose neck was observed and in whom lymph node metastases became apparent subsequently were salvaged with surgery and, in most instances, radiation and/or chemotherapy. This remarkable result is probably due to the strict follow-up, which consisted of monthly evaluations for the first year and US examination of the neck every 3 months for the first 3 years.[61,62]

In patients with cancer of the larynx, a study by Gallo et al.[16] retrospectively compared a group of 76 patients who underwent elective neck dissection and were found to have histologically positive nodes with a group of 96 patients, who were initially staged N0, but subsequently developed lymph node metastases and underwent therapeutic neck dissection. After a minimum follow-up of 5 years, they found no statistically significant difference between the two groups of patients in overall, determinant, and actuarial survival rates. Other retrospective studies have found that elective neck dissection decreases the neck recurrence rates significantly in patients with supraglottic carcinoma.[63]

Self-examination by the patient and reliable follow-up are essential for watchful waiting to succeed in the management of the N0 neck. Unfortunately, a significant number of the patients who do not undergo elective neck dissection cannot be salvaged later, when they present with palpable metastases, because the cancer process is too far advanced. In a review of 122 patients with T3/T4N0 cancers of the larynx that were treated by total laryngectomy and observation of the neck at the University of Hong Kong, 36% of the patients who later presented with palpable metastases had inoperable cancer and were amenable to palliative treatment only. Furthermore, of the patients who were operable, 42% eventually died of a recurrence in the neck. These observations, in combination with the idiosyncrasies of character and social background of many patients who have cancer of the head and neck, are the reason why most head and neck surgeons prefer to treat the neck electively, even though the impact of this decision on patient survival remains somewhat controversial.

Type of Neck Dissection

A SND is currently the preferred type of neck dissection for the elective surgical management of the neck in patients with squamous cell carcinomas of the upper aerodigestive tract. These operations consist of the removal of only the lymph node groups at highest risk of containing metastases according to the location of the primary tumor while preserving the SAN, the IJV, and the SCM.

The concept of SND was developed on the basis of the following observations:

1. Patterns of lymph node metastases: Anatomic, pathologic, and clinical investigations[41,64–74] as well as recent prospective studies[75,76] have demonstrated that cervical lymph node metastases occur in predictable patterns in patients with SCCs of the head and neck.

The lymph node groups most frequently involved in patients with carcinomas of the oral cavity are the nodes in levels I and II. The nodes in level Ia are frequently involved in patients with carcinoma of the floor of the mouth and anterior oral tongue. These cancers frequently metastasize to both sides of the neck, and they can skip levels I and II, metastasizing first to the nodes in level III. In a retrospective study of 1,119 RNDs, Shah[71] found that cancers of the oral cavity metastasized most frequently to the neck nodes in levels I, II, and III, whereas carcinomas of the oropharynx, hypopharynx, and larynx involved the nodes in levels II, III, and IV.

It has been demonstrated that in the absence of metastases to the first-echelon nodes, cancers of the oral cavity and oropharynx rarely involve the nodes in level IV and level V. The nodes in level V are not commonly involved, regardless of the site of the primary tumor and whether in the presence or absence of metastases in the jugular nodes,[77] conceivably because there is no retrograde flow from the jugular nodes into the spinal accessory nodes.

Similarly, in a prospective analysis of the prevalence and distribution of histologic lymph node metastases in 100 consecutive neck dissections done as part of the initial treatment of laryngeal and hypopharyngeal cancer, Buckley and MacLennan[76] found that all metastases in N0 and N1 cases were confined to levels II, III, IV, and VI. Metastases to levels I and V were infrequent, even in N+ disease, and occurred only in cases with N2c and N3 disease. These results support the use of dissection of node levels II to IV for N0 and selected N+ cases with laryngeal and hypopharyngeal cancer.

Outcomes: A number of retrospective studies have shown that when SND is used for the elective treatment of the regional lymphatics, regional control and survival rates are similar to those of more extensive neck dissections.[53,78–87] Furthermore, two multi-institutional prospective randomized studies comparing SND to MRND were performed by the Brazilian Head and Neck Cancer Study Group. The first study[88] compared SOHND (SND I to III) with MRND in patients with cancer of the oral cavity and clinically N0 neck. The regional control and overall 5-year actuarial survival rates were 87.5% and 67.0% for the SOHND group versus 89.5%

and 63.0% for the MRND, respectively. The differences were not statistically significant. The second study compared MRND type III and lateral neck dissection (SND II to IV) in patients with supraglottic and transglottic carcinomas. The rates of 5-year overall survival, neck recurrences, and complications were similar in both groups.

Morbidity: SNDs result in less postoperative morbidity. The dysfunction of the trapezius muscle produced by SNDs is minimal and, unlike that produced by the RND, is usually temporary and reversible.[89–94]

The type of SND recommended for the management of the N0 neck depends on the site of the primary cancer.

Oral Cavity

SND of level I to III or ND (I to III) (commonly referred to as "supraomohyoid" neck dissection) (Fig. 18.7) and SND of levels I to IV or ND (I to IV) (also referred to as "extended supraomohyoid" neck dissection) are commonly used in the surgical treatment of patients with SCC of the oral cavity. The lymph nodes removed are those contained in the submental and submandibular triangles (level I), the upper jugular region (level II), and the midjugular region (level III). The posterior limit of the dissection is marked by the cutaneous branches of the cervical plexus and the posterior border of the SCM. The inferior limit is the omohyoid muscle as it crosses the IJV. These operations have been described in detail by Medina and Byers.[95] The procedure is performed on both sides of the neck in patients with cancers of the anterior tongue and floor of the mouth.

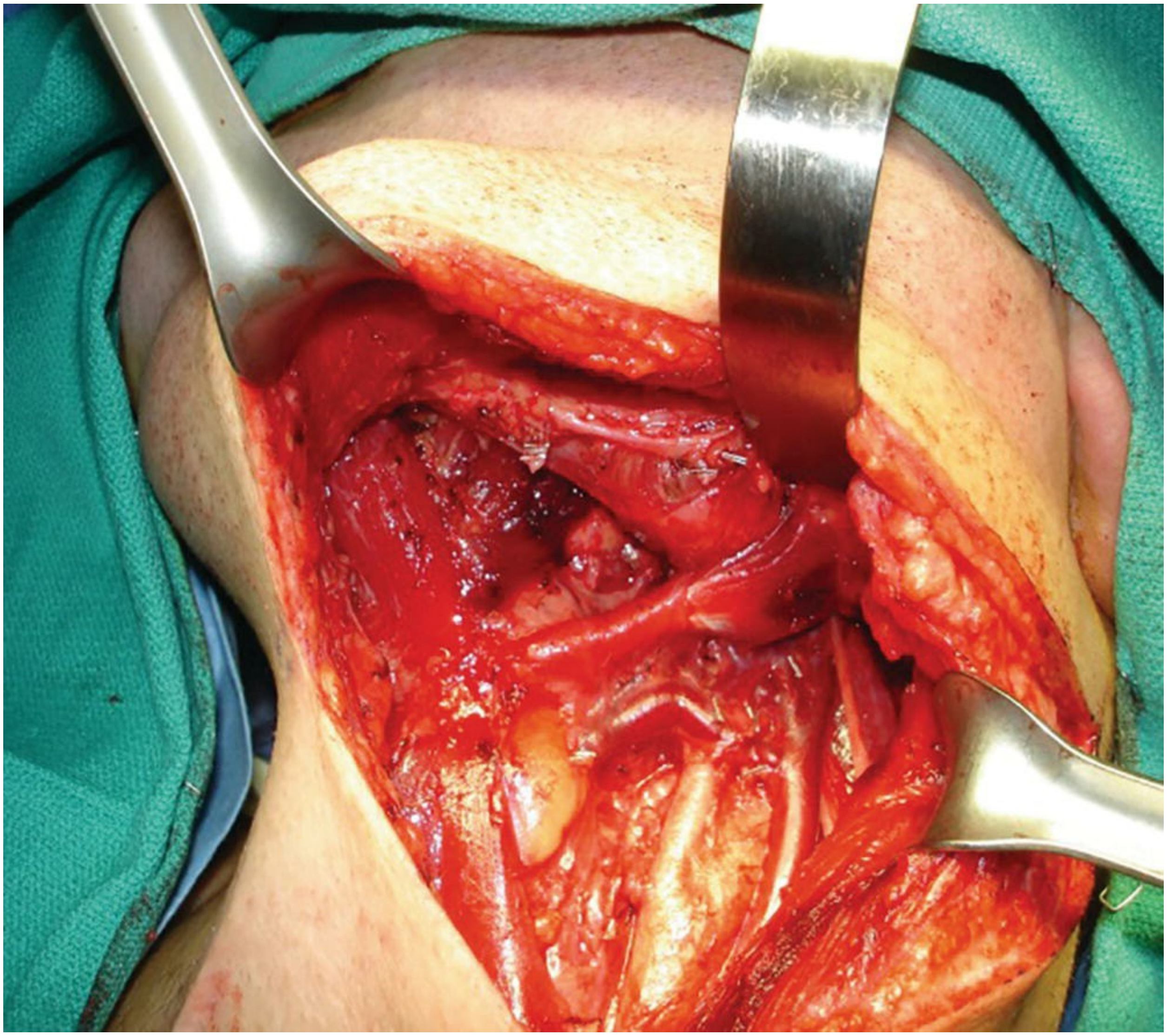
Figure 18.7. Selective neck dissection of lymph node levels I to III (supraomohyoid neck dissection).

The need to routinely remove the nodes in level IV in patients with cancer of the oral tongue is controversial. Byers et al.[64] reported finding "skip metastases" in 15.8% of patients with oral tongue cancer. In these cases, metastases to either level III or IV were the only manifestation of metastasis in the neck. In a similar, more recent review of 119 neck dissections in patients with cancer of the oral cavity, De Zinis et al.[96] found metastases in level IV nodes in 15% of the patients and 28% of them were skip metastases. In another study of 49 patients with cancer of the oral cavity, staged N0, undergoing "extended supraomohyoid" neck dissection, occult metastasis in level IV were found in 10% of the cases.[97] These and other authors contend

that the supraomohyoid neck dissection is inadequate for a complete pathologic evaluation of all the nodes at risk, and they recommend dissecting the nodes in level IV when performing an elective neck dissection in patients with cancer of the oral tongue.

The opposing point of view has been advanced by Khafif et al.[98] whose practice has been to dissect level IV only when a suspicious node is found at level III or there are multiple obviously involved lymph nodes in level II, III, or both. They reported their findings in a cohort of 58 patients with squamous cell carcinoma of the oral tongue (stage T1/T2 N0). The node dissections performed included levels I through III in 42 patients (69%), levels I through IV in 16 patients (26%) and levels I through V in 1 patient (5%). A positive node was found in level IV in only one instance (1/54, 1.8%), and no recurrences were observed in level IV. Ambrosch et al.[78] reported similar observations in a study of 167 patients with cancer of the oral cavity and oropharynx of whom 82 had a clinically staged N0 neck. They dissected level IV only when multiple metastases were suspected during the neck dissection. At a median follow-up of 34 months, the rate of regional recurrence in that series was 5.4%. Shah et al.[72] studied RND specimens performed as elective treatment for cancers of the oral cavity and found metastatic involvement of level IV in 3% of the patients. Li et al.[99] studied 153 patients who had a RND for cancer of the oral cavity (60 therapeutic and 93 elective) and found metastases to level IV in 3.2% of the patients. Wang et al.[100] studied 116 patients with cancer of the oral tongue, staged N0, who underwent comprehensive neck dissections and 5 patients who had SND. Metastases in levels IV or V were found in only one patient each. Interestingly, there were five cases with level III involvement as a first echelon of metastasis. These studies and others[101] have shown that the risk of metastases to level IV in patients with cancer of the oral tongue with clinically negative neck is low; thus, the controversy about the routine inclusion of this level in END in such patients remains.

Cancer of the Larynx and Pharynx

An SND of levels II to IV or ND (II to IV) (Fig. 18.8), commonly referred to as the “lateral” neck dissection, is used in the treatment of patients with cancer of the larynx, oropharynx, and hypopharynx. It consists of the removal of the upper (level II), middle (level III), and lower (level IV) jugular lymph

nodes. For cancers of the supraglottic larynx and posterior pharyngeal walls, the dissection is often bilateral. A recent description of the technique of this operation has been provided by Khafif.[102]

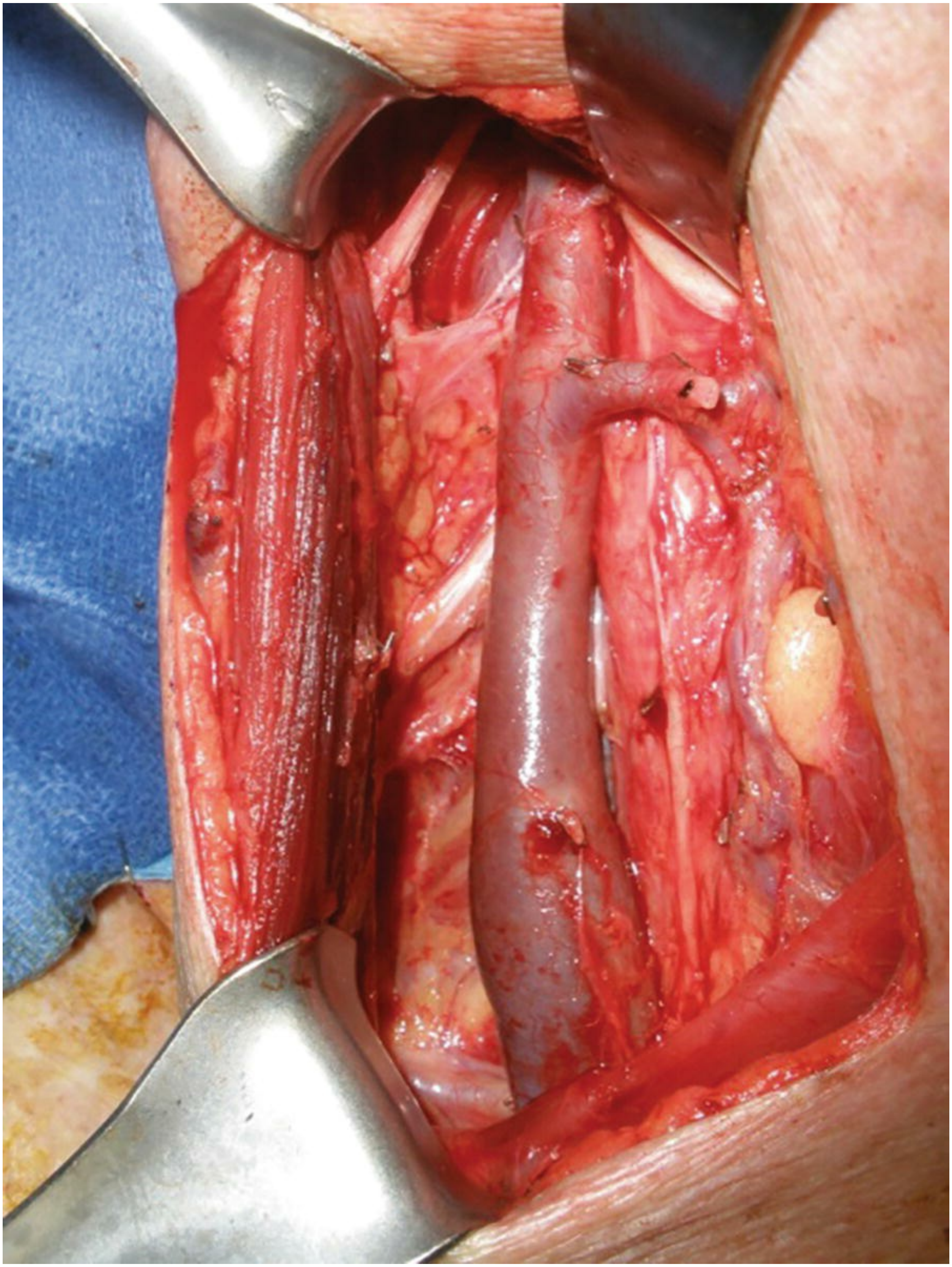

Figure 18.8. Selective neck dissection of lymph node levels II to IV (lateral

neck dissection).

The need to dissect the lymph nodes of sublevel IIB and level IV in every patient undergoing elective SND for cancer of the larynx has recently been questioned. In 2006, Rinaldo et al.[103] collected data from five prospective, multi-institutional studies of neck dissection specimens using pathologic and molecular analysis. These studies included 211 patients with cancer of the larynx and clinically N0 neck. Only three patients (1.4%) were found to have positive lymph nodes at sublevel IIB (one patient had also lymph node metastases to sublevel IIA and level III; the other two patients had also a positive lymph node at sublevel IIA). In a more recent prospective multi-institutional study, metastases in sublevel IIB nodes were found in only 2% of 92 neck dissections done for laryngeal cancer.[104] This and other recent studies have shown that the incidence of sublevel IIB metastases in patients undergoing elective neck dissection for cancers of the hypopharynx and oropharynx is also low, ranging between 5% and 9% for hypopharynx cancer and between 0% and 6% for oropharynx cancer.[50,104,105] These observations strongly suggest that dissection of sublevel IIB is not necessary in patients with cancer of the larynx, oropharynx, and hypopharynx and a clinically N0 neck. Because dissection of this region requires, in most patients, a more extensive manipulation of the SAN, avoiding it can decrease operative time and the risk of postoperative dysfunction of this nerve, as it has been suggested by a recent study using electromyography.[51]

The need to dissect level IV electively in patients with cancer of the larynx has also been questioned recently. In a review of 43 patients with laryngeal SCC who underwent elective ND of levels II to IV, Khafif et al.[52] found that only one patient (2.3%) had metastases in level IV nodes and that patient also had metastases in level II nodes. Others have made similar observations indicating that the prevalence of positive nodes found in level IV in the absence of palpable metastases elsewhere in the neck varies from 0% to 2.3%.[53,106] Furthermore, a recent analysis of the data from three prospective multi-institutional studies of neck dissection specimens, including 175 patients with cancer of the larynx and clinically N0 necks, revealed only 6 patients (3.4%) with positive lymph nodes in level IV.[107,108] Based on a thorough review of prospective multi-institutional studies published to date, Ferlito et al.[109] concluded that dissection of sublevel IIa

and level III appears to be adequate for the elective surgical treatment of the neck in cancer of the supraglottis and glottis. Appropriate outcomes studies are now needed to ascertain that not dissecting these areas of the neck will not have a negative effect on regional control of the disease.

Other lymph node groups that need to be considered when managing cancers of the larynx and pharynx are the retropharyngeal (RPLN) and the paratracheal lymph nodes (PTLNs).[110]

Retropharyngeal Lymph Nodes

In general, the RPLNs do not need to be addressed when managing a neck otherwise staged N0. In a retrospective study designed to assess the frequency of RPLN metastases in 774 patients with SCC of the nasopharynx, oropharynx, hypopharynx, and supraglottis, using enlargement of the RPLN on CT scans as an indicator of the presence of metastases, McLaughlin et al.[111] found an overall incidence of radiologically “positive” RPLN of 9% of the patients. The highest incidence was seen in patients with cancer of the nasopharynx (74%) and the pharyngeal walls (19%). They also noted that in patients with advanced cancer of the walls of the oropharynx and hypopharynx, the incidence of radiologically positive RPLN was higher in patients with cervical metastases (N+ necks) than in those with an N0 neck (pharyngeal wall, N+ 21%, N0 16%; hypopharynx, N+ 9%, N0 0%).[111] Amatsu et al. studied 82 patients who had RPLN dissection for squamous cell carcinoma of the hypopharynx and cervical esophagus and reported finding metastases in the RPLN in 16 patients (20%).[112] Fourteen of these patients had cancer of the hypopharynx, and the posterior pharyngeal wall was involved in 57% of them. In keeping with the studies mentioned previously, the majority of patients with RPLN metastases also had metastases in neck nodes at other levels. However, in 15% of the patients with RPLN metastases, the neck was staged N0.[112]

Paratracheal Lymph Nodes

The paratracheal lymph nodes (PTLN) are a common site of metastases from cancers of the larynx that involve the subglottic region and for cancers of the cervical esophagus. In a study that included 91 patients with carcinoma of the larynx who underwent paratracheal lymph node dissection, Weber et al.

found that metastases to these lymph nodes occurred more often in patients with subglottic cancers (40%) and transglottic cancers (21.4%), but they also occurred in patients with cancer of the glottis (13%) and supraglottis (15.7%). The presence of PTLN metastases had a significant negative impact on survival. Although the survival at 48 months for the entire group of 141 patients was 60%, none of the 29 patients with PTLN metastases survived beyond 42 months (p > 0.0.001).[113] In 2005, Plaat et al. performed a retrospective study of 85 patients who underwent total laryngectomy and PTLN dissection for cancer of the larynx and hypopharynx. The prevalence of PTLN metastases was 30%, 12%, and 67%, in patients with supraglottic, glottic, and subglottic carcinomas, respectively. Among all carcinomas of the larynx with subglottic extension, PTLN metastases were found in 27% of the cases.[114]

Based on the anatomy of the lymphatic drainage of the different laryngeal sites and on the pertinent clinical observations described in the literature, dissection or treatment with radiation of the lymph nodes in level VI is indicated in the following situations[115]:

1. Primary carcinomas of the subglottis. Treatment/dissection in these cases should include the pretracheal and the paratracheal nodes on both sides.
2. Advanced (T3/T4) carcinomas of the glottis particularly those with involvement of the anterior commissure and with subglottic extension. In cancers confined to one side of the larynx, treatment/dissection should include the prelaryngeal, the pretracheal, and the ipsilateral paratracheal nodes. In cancers involving both sides of the larynx, treatment should include the paratracheal lymph nodes on both sides.
3. Advanced (T3/T4) carcinomas of the supraglottis, particularly those with involvement of the ventricle/paraglottic space, the anterior commissure, and those with clinically apparent lymph node metastases in the lateral compartment of the neck. In cancers confined to one side of the larynx, treatment/dissection should include the prelaryngeal, the pretracheal, and the ipsilateral paratracheal nodes. In cancers involving both sides of the larynx, treatment should include the paratracheal nodes on both sides.

In these situations, a neck dissection should be extended to include the paratracheal and pretracheal lymph nodes; failure to do so may predispose to the development of peristomal recurrence. It should also be emphasized that the presence of metastases in PTLN has been found to be associated with

increased tumor recurrence.[115]

Postoperative Adjuvant Therapy

In patients with a clinically N0 neck, the neck dissections also serve as a staging procedure. Information provided by the histopathologic examination of the lymph nodes is used for decision making regarding the need for adjuvant postoperative therapy. If the lymph nodes are histologically negative, no further therapy is indicated and the patient is treated with surgery alone. However, to make this decision with confidence, all the lymph nodes at risk of containing metastases must be evaluated. This evaluation requires dissecting both sides of the neck in patients with lesions of the anterior tongue and floor of the mouth, supraglottic larynx, and most oropharyngeal and hypopharyngeal cancers.

If the histopathology indicates that there is metastases in lymph nodes, adjuvant therapy is considered, and the type of therapy depends on the number of nodes involved and on whether or not the cancer extends beyond the capsule of the lymph nodes.

Pathology Staging N_1 (pN_1)

When a single metastasis is found (pN_1) in a neck dissection specimen, surgery alone has been considered adequate treatment. However, regional recurrence rates from 16% to 25% have been reported with surgery alone, and it has been suggested that postoperative radiation may be beneficial.[53,116]

In a retrospective analysis of 517 SNDs performed in 363 patients, Byers et al. found 51 (17.6%) patients who had metastases in only one lymph node (pathologically N1) with or without ECS. A regional failure occurred in 2 of 36 (5.6%) of these patients who received postoperative radiation and in 5 of 14 patients (35.7%) who did not. All recurrences were within the dissected area of the neck.[53] More recently, Chen et al. analyzed 59 patients with T1–T2/N0–N1 SCC of the oral cavity to determine the effect of postoperative radiation. Of the patients staged pathologically N1, 28 received postoperative radiation and 31 did not. With a mean follow-up period of 46 (12 to 121) months, locoregional recurrences occurred in 14% of the patients that received postoperative radiation and in 39% of the patients who did not. As in the Byers' study, all regional recurrences occurred within the dissected

neck. To characterize further the impact of the N1 status and radiation, the authors excluded from the analysis patients with ECS, positive margins, lymphovascular invasion, and perineural invasion and compared those that had received post-operative XRT with those that did not. The 5-year disease-free survival rate and overall survival were 95% and 92.3%, respectively, for the group that received postoperative radiation and 54.7% and 54.9%, respectively, for the group that did not.[117] However, radiation was found not to be beneficial in an unpublished retrospective review that we conducted of 58 patients with T1/T2 squamous cell carcinoma of the oral tongue treated with surgery, which included an ipsilateral SND and was found to have metastasis in a single lymph node. These patients were treated at 7 institutions and were followed for a minimum of 2 years. Twenty-two (38%) patients were treated with surgery alone, whereas 36 (62%) received postoperative radiation. In the group treated with surgery alone, two patients had recurrence at the primary site and in the neck. Of the remaining 20 patients, 6 (30%) recurred in the neck (5 contralateral and 1 simultaneous ipsilateral and contralateral). In the surgery plus radiation group, 4 (11%) tumors recurred in the neck, all within the operative field. The difference in the rate of recurrence in the neck for the two groups was not statistically significant.

Thus, it appears that a prospective randomized study is necessary to determine in a controlled manner whether or not postoperative radiation is beneficial in patients whose neck is pathologically staged N1. The Radiation Therapy Oncology Group is currently accruing patients to evaluate this question further, in RTOG 0920 Protocol: A Phase III Study of Postoperative Radiation Therapy (IMRT) +/− Cetuximab for Locally Advanced Resected Head and Neck Cancer.

Pathology Staging N2/N3 (pN2-3)

When lymph node metastases are multiple or the cancer extends beyond the capsule of a lymph node, a neck dissection alone is associated with a high incidence of recurrence in the neck.[71,118,119] In these situations, the addition of postoperative radiation therapy results in better regional control of the disease, as demonstrated in numerous studies.[120–123] In addition, it has also been accepted that timing of the initiation of radiotherapy is important, as delays beyond 6 weeks may compromise tumor control.[122] Regarding the

dose of radiation therapy in the postoperative setting, a seminal study by Peters et al.[124] in the early 1990s established that a total dose of 57.6 Gy, delivered to the entire operative bed in daily fractions of 1.8 Gy, is necessary to achieve optimal results; for areas at higher risk for recurrence, such as areas of the neck where extracapsular spread of cancer was found, the ideal dose is 63 Gy.

A prospective, randomized clinical study published in 2004 showed that the concurrent postoperative administration of chemotherapy (cisplatin 100 mg/m^2 on days 1, 22, and 43) and radiotherapy (60 to 66 Gy in 30 to 33 fractions over 6 to 6.6 weeks) significantly improved the rates of local and regional control and disease-free survival in patients with high-risk–resected cancers of the head and neck.[125] The high-risk criteria included any or all of the following: histologic evidence of metastases in two or more lymph nodes, ECS, and microscopically involved margins of resection. Although the subjects of the study were stratified according to the presence or absence of microscopically positive margins, the published results did not include an analysis of outcomes with and without concomitant chemotherapy in the cohort of patients with microscopically negative margins, which would have helped to understand whether or not the addition of chemotherapy was beneficial to patients with high-risk neck metastases. A similar study by the European Organization for Research and Treatment of Cancer, published at the same time, included patients with various clinical (primary cancer and nodal volume and nodal site) and pathologic (involved margins of resection, ECS, perineural involvement, and vascular embolism) high-risk factors related to neck metastases.[126] It also showed that concomitant postoperative chemoradiation was significantly more efficacious than radiation alone in these high-risk patients. However, resection margins were positive in 30% of the patients included in the study, and the design did not include an analysis focused on the neck disease factors. Nonetheless, both of these studies suggested that the addition of chemotherapy may be beneficial to patients with resectable cancers of the head and neck who have advanced metastases to the neck (N2/N3) and to patients with N0 or N1 disease who are found to have multiple histologically positive nodes or extracapsular spread.

In a subsequent analysis of both the EORTC and RTOG studies, Bernier et al. found that chemoradiation improved overall survival in patients with ECS and/or positive margins in the EORTC study ($p = 0.0019$), but the

improvement did not reach statistical significance in the RTOG study (p = 0.0.63).[127,128] Thus, in regard to adjuvant treatment of neck metastases following neck dissection, the presence of extracapsular spread is currently considered an indication for postoperative concurrent chemoradiation.

Primary Cancer Treated with Radiation with or without Chemotherapy

In many centers today, cancers of the oropharynx, larynx, and hypopharynx are initially treated with either radiation alone (T1 and T2 cancers of the oropharynx, larynx, and hypopharynx) or combinations of radiation and chemotherapy (T3 cancers of the oropharynx, larynx, and hypopharynx). In these patients, the likelihood of subclinical metastases in the lymph nodes is sufficiently high to warrant elective treatment of the neck. Several studies have shown that elective radiation results in a >90% control rate of micrometastasis.[129] In a more recent study of a large cohort of patients with carcinoma of the oropharynx treated at MD Anderson Cancer with intensity-modulated radiation therapy (IMRT), which included 88 patients with N0 neck staging, only 4 patients (4.5%) developed a recurrence in the neck.[130]

MANAGEMENT OF THE N+ NECK

As with the N0 neck, the initial management of the neck when lymph node metastases are clinically apparent is also dictated by the initial treatment modality chosen for the primary cancer.

Primary Cancer Treated with Surgery

When surgery is the initial treatment of the primary cancer, initial management of the “positive” neck consists of a neck dissection. The purpose of the operation is to adequately remove the disease present in the neck. Decades ago, surgeons performed only one operation when managing the “positive” neck, for example, a RND. Today, the extent of the operation, that is, the type of neck dissection, is dictated by the extent of the metastases to the neck.

ND (I to V, SCM, IJV, XIN) (Radical Neck Dissection)

A RND is indicated when there are multiple clinically obvious cervical lymph node metastases, particularly when they involve the lymph nodes of the posterior triangle of the neck and are found to surround or to be tightly adherent to the SAN. A RND is also indicated when there is a large metastatic tumor mass or when multiple matted nodes are present in the superior aspect of the neck. In such instances, it is unwise to preserve the sternocleidomastoid or the internal jugular or to dissect the SAN and risk entering the cancer (Fig. 18.9). A similar situation can be created by the inflammation, hematoma, or ecchymosis that follow ill-advised excisional biopsies of neck metastases. A RND may be the safest option in such patients. Currently, RNDs represent <20% of all neck dissections done at many institutions.[131] A comprehensive description of the surgical technique of this operation was recently provided by McCammon and Shah.[132]

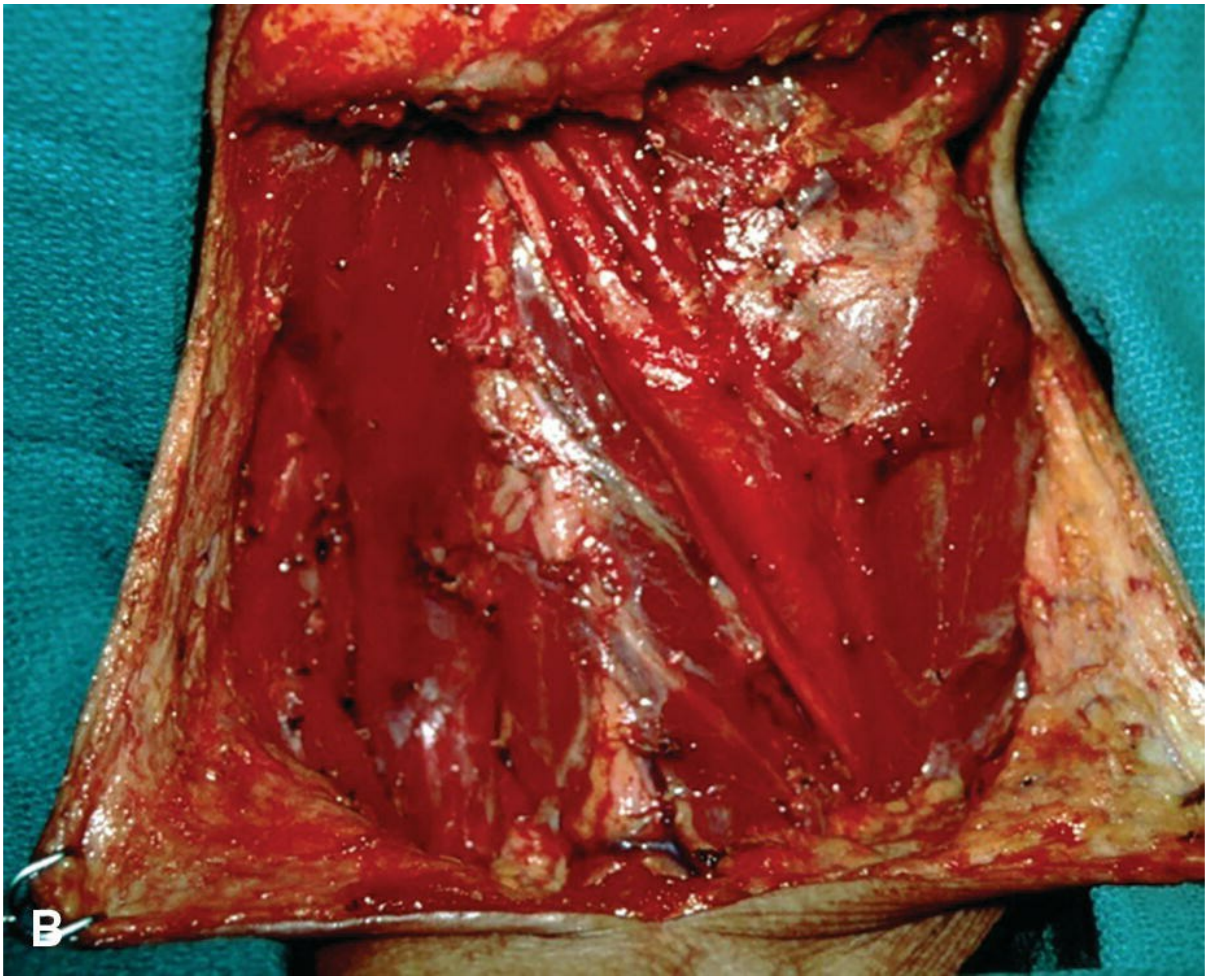

Figure 18.9. A: Patient with multiple matted nodes in the upper and midportions of the neck. **B:** Radical neck dissection.

ND (I to V, SCM, IJV) (Modified Radical Neck Dissection with Preservation of the Spinal Accessory Nerve)

When the metastatic lymph nodes grossly involved by cancer are not in close proximity to the SAN, preserving the nerve does not compromise the oncologic soundness of the operation and may prevent shoulder morbidity associated with resection of the nerve.

This type of neck dissection (Fig. 18.10) is used in the surgical treatment of the neck of patients with clinically obvious lymph node metastases when the SAN is not directly involved by cancer, regardless of the number, size,

and location of the involved lymph nodes. The decision to preserve the SAN is, therefore, a delicate intraoperative surgical decision. Much like the philosophy about preservation of the facial nerve during surgery for parotid tumors, the SAN can be preserved whenever there is a clearly identifiable, not an artificially created, plane of dissection between the tumor and the nerve knowing that the patient will be treated with radiation or chemoradiation postoperatively. The reported rate of recurrence in the neck when used for the treatment of the N+ neck in combination with postoperative radiation is 8.1%.[133]

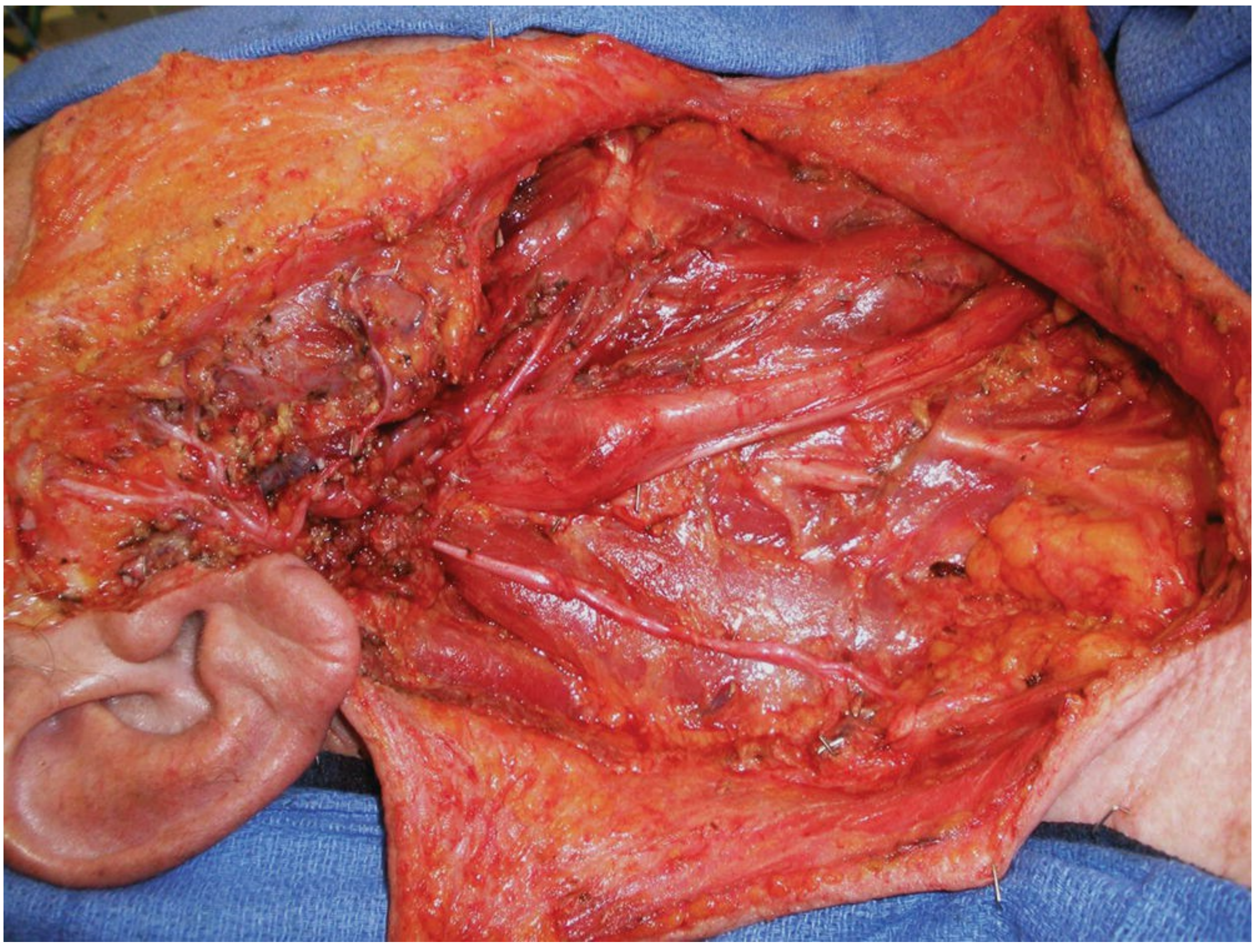

Figure 18.10. ND (I to V, SCM, IJV) (Modified radical neck dissection with preservation of the SAN).

ND (I to V, SCM) (Modified Radical Neck Dissection with Preservation of the Spinal Accessory Nerve and the

Internal Jugular Vein)

In this type of dissection, the lymph node–bearing tissues of one side of the neck are removed en bloc, preserving the SAN and the IJV (Fig. 18.11). This operation is seldom planned. It is done occasionally when, in the course of a neck dissection, the metastatic cancer in the neck is noted to be adherent to the SCM but not directly involving the accessory nerve and the jugular vein. This situation occurs occasionally in patients who have cancer of the hypopharynx or larynx with metastases deep to the middle third of the SCM.

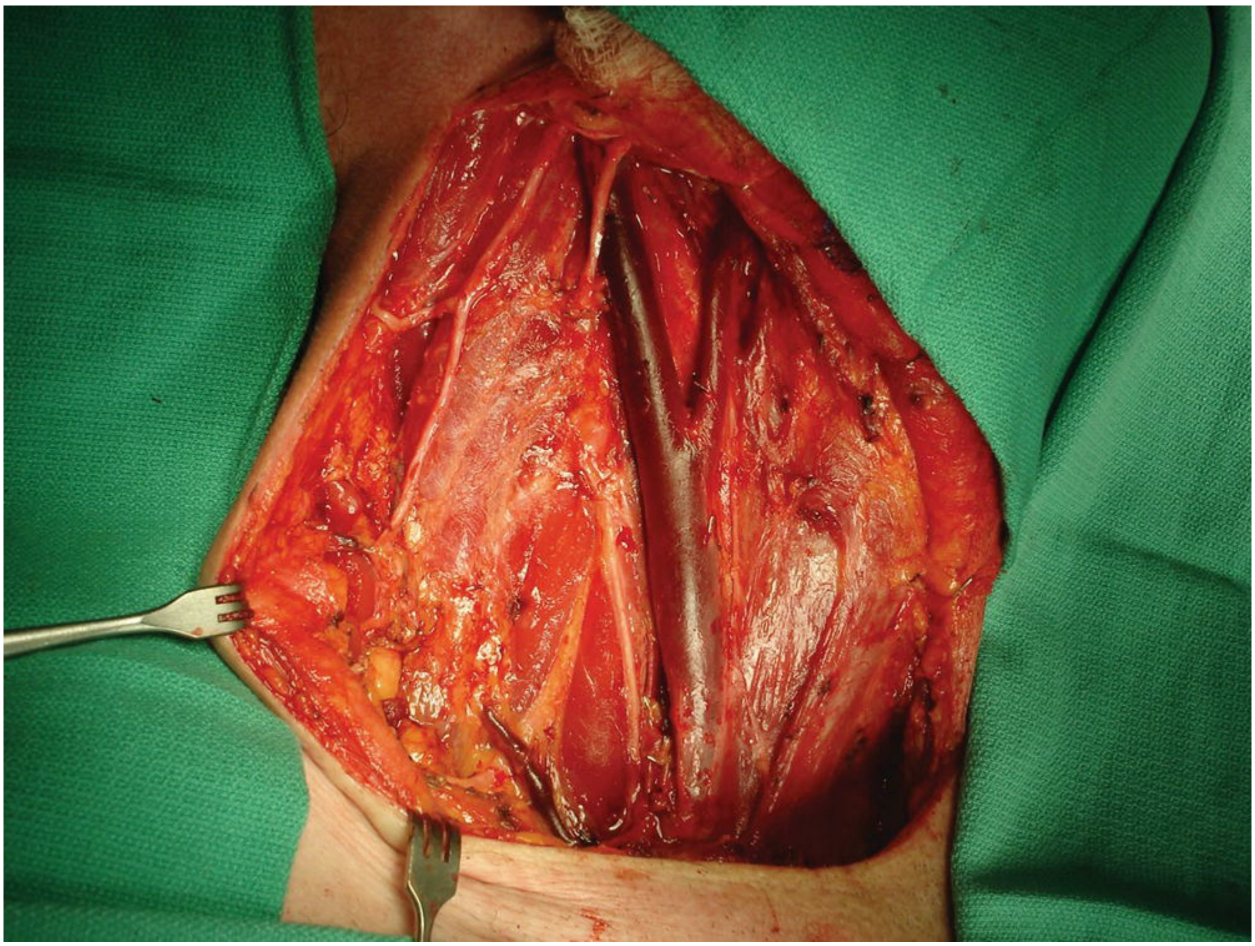

Figure 18.11. ND (SCM) (Modified radical neck dissection with preservation of the SAN and the IJV).

ND (I to V, SCM, IJV, CN XI) (Modified Radical Neck Dissection with Preservation of the Spinal Accessory Nerve, the Internal Jugular Vein, and the

Sternocleidomastoid Muscle)

In the early 1960s, Suárez[134] observed that the lymph nodes of the neck are not located within the muscular aponeurosis of the SCM and do not form part of the adventitia of nearby blood vessels, particularly veins. He also demonstrated that it was technically feasible and oncologically sound to perform a comprehensive removal of the lymph node–bearing tissues of one or both sides of the neck without removing the SCM, the submandibular gland, and the IJV. It should be pointed out that the nerves of the neck do not follow the aponeurotic compartment distribution, except for the vagus nerve, which is contained within the carotid sheath. The phrenic nerve and the brachial plexus are partially within a compartment; the hypoglossal and the SANs run across several compartments. Unless these nerves are directly involved by cancer, they can be dissected free and preserved (Fig. 18.12).

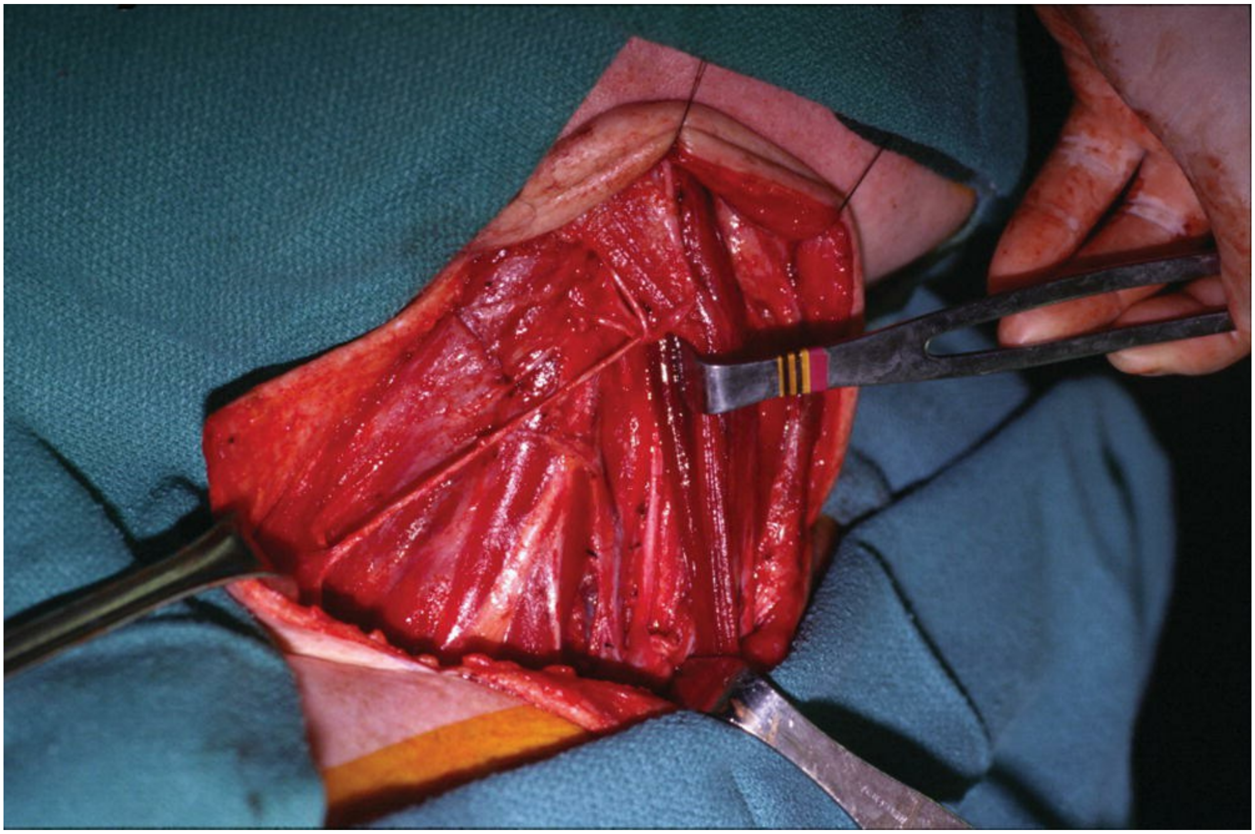

Figure 18.12. ND (I-V, SCM, IJV, CN XI) (Modified radical neck dissection with preservation of the SAN, the IJV, and the SCM).

A description of this operation, as it is currently advocated by most

European surgeons, can be found in a publication by Gavilan et al.[135] According to some surgeons, this operation is indicated for the treatment of the N1 neck, when there are multiple metastatic nodes that are mobile and no >2.5 to 3 cm. The reported rates of recurrence in the neck with this type of neck dissection range between 3.7% and 25% for the N+ neck.[134–139]

Selective Neck Dissection

SND is being used with increasing frequency in the management of selected patients with clinically obvious lymph node metastases (N+). In order to determine the feasibility of doing a supraomohyoid neck dissection in patients with carcinoma of the oral cavity who have a single clinically metastatic lymph node smaller than 6 cm (N1 and N2a), Kowalski and Carvalho[69] studied a series of patients with cancer of the oral cavity with clinical stage N1 or N2a cancer submitted to RND. Interestingly, metastases were found in any level IV lymph nodes in only one patient (0.6%), and metastases were not found in level V nodes. The authors concluded that in patients with clinical stage N1 in whom the metastasis is at level I, a supraomohyoid neck dissection (extended or not to level IV) is feasible instead of a RND.[74] Andersen et al.[136] reported a 10-year multi-institutional retrospective review of pooled data from 106 previously untreated clinically and pathologically node-positive patients who went under 129 SNDs and followed for a minimum of 2 years or until death. The neck was clinically staged N1 in 58 patients (57.7%), N2a in 5 (4.7%), N2b in 28 (26.4%), N2c in 14 (13.2%), and N3 in 1 (0.9%). Extracapsular extension of tumor was present pathologically in 36 patients (34.0%), and postoperative radiation therapy was administered to 76 patients (71.7%). Overall, nine patients had recurrence in the neck. Six of these recurrences were in the areas of the neck that had been dissected during the SND, for a regional recurrence rate of 5.7%. The recurrence rates reported by others using SND in the N+ neck ranges from 5.5% to 11.1% (mean recurrence rate of 8.3%).[137,138]

The recurrence rates following SND are comparable to those reported after MRND or RND.[133,139–144] Patel et al.[145] reported the results of a comparison of outcomes following therapeutic SND and comprehensive neck dissections. This study involved a retrospective review of 232 therapeutic neck dissections with a minimum of 2 years follow-up. Patients having SND had fewer adverse prognostic factors compared with patients having

comprehensive dissection ($pN_{2\text{-}3}$, $p = 0.001$; and extracapsular spread, $p = 0.001$). In spite of this, there was no significant difference between the two groups in regional control in the dissected neck (96% vs. 86%, $p = 0.06$), and disease-specific survival (59% vs. 43%, $p = 0.06$).

These observations suggest that SND can be used to effectively treat the clinically positive neck in selected patients with squamous cell carcinoma of the upper aerodigestive tract.

Extended Neck Dissection

Sometimes, the extent of the metastatic cancer in the neck is such that adequate removal requires the neck dissection to be "extended," to include either structures that are not routinely removed (i.e., skin of the neck, carotid artery, levator scapulae, vagus or hypoglossal nerve) or lymph node groups that are not routinely removed (i.e., retropharyngeal, paratracheal, upper mediastinal).

Skin, Muscles, and Nerves

In a review of 106 cases of extended neck dissections, the largest review on record in the literature, involvement of the skin occurred in 18% of cases.[146] Involvement of the skin did not have a significant prognostic implication.

Involvement of muscles requiring extension of the neck dissection may include superficial, prevertebral, and paraspinal muscles. The superficial group is composed of the strap muscles (sternohyoid, sternothyroid, and omohyoid), the mylohyoid, and the digastric/stylohyoid muscle complex. Removal of one or more of these muscles was the reason for extending neck dissections in as many as 62% of the cases studied by Carew and Spiro,[146] the digastric muscle being among the structures sacrificed in 51% of cases. The functional deficit resulting from removal of these muscles is of little consequence functionally, and their removal usually does not typically require reconstruction. The dissection was extended to include the prevertebral muscles in only 3% of the cases. The muscles deep to the sternocleidomastoid that may be involved by a cancer are the splenius capitis, the levator scapulae, and the semispinalis capitis muscles. Involvement of these muscles occurs most commonly just lateral to the carotid artery. It was the reason to extend a neck dissection in 14% to 18% of cases.

Cancers may be adherent to or involve several important nerves in the neck. Because the lymph nodes in level II are the most common site of metastases, the nerve most commonly involved is the hypoglossal nerve (41%). This is followed by the sympathetic chain (8%), the lingual nerve (7%), the vagus nerve (4%), the superior laryngeal nerve (3%), the phrenic nerve (3%), and the glossopharyngeal nerve (2%).[146] When a nerve is resected, it is advisable to obtain an intraoperative frozen section of the margins of resection even if the appearance of the nerve is normal; perineural tumor spread is initially axial and may not result in thickening of the nerve until late.[147]

The Carotid Artery

Controversy still exists about the advisability of extending a neck dissection to resect the common or the internal carotid artery. Initial reports on resection of the carotid artery showed very poor results, with ~50% of patients suffering either a severe stroke or death. Recent reports have shown a decrease in these events to ~25%, with modest improvement in survival compared to those who did not undergo resection. This is epitomized by the recent report by Freeman et al.[148] of their experience with 58 patients with metastatic lymph nodes adherent to the internal or common carotid artery. Angiography was used in patients who demonstrated fixation of tumor to the carotid artery on examination or imaging, followed by balloon test occlusion and single photon emission computer tomography (SPECT) brain scanning. In most patients (70%), the carotid was reconstructed with a vein graft, especially if there was insufficient collateral cerebral circulation. In addition, these patients were given 15 to 20 Gy of intraoperative radiation. In their more recent cases, the carotid was permanently occluded preoperatively when possible. Unfortunately, in spite of such aggressive treatment preceded by a systematic, "state-of-the-art" preoperative assessment, the median disease-specific survival was 12 months and 11 patients (19%) suffered a stroke.[148] The mean 1-year disease-free survival rates reported in the literature after resection and reconstruction of the carotid varies between 0% and 44%.[149]

When considering resection of the carotid artery, the surgeon must make critical preoperative, intraoperative, and postoperative decisions. Preoperative evaluation of these patients requires a clear understanding of the methods available for assessment of the cerebral circulation. Several tests are available

that involve occlusion of the carotid artery with either digital pressure (Matas test) or using a balloon during arteriography. The objective of each method is to determine a "critical point" that indicates when reconstruction of the artery is necessary. With the transcranial color Doppler method, the "critical point" is reverse flow from the external carotid artery to the internal carotid. Technetium-99m hexamethylpropyleneamine oxime brain SPECT measures cerebral perfusion. A 19% to 29% reduction in radioactivity is considered the "critical point." Unlike some of the other methods, this is not a real-time measurement, but requires delayed imaging. Another method uses Xenon in an aerosolized mixture that is inhaled by the patient, and then cerebral perfusion is measured by CT scan. Xenon is concentrated in areas of the brain that are well perfused, correlating with blood flow. Two CT scans are obtained to assess cerebral blood flow, the first one during balloon occlusion and the second after the balloon is released. The "critical point" is a 25% reduction in the degree of enhancement on the first occlusion scan compared to the open study. Electroencephalography (EEG) has a distinct disadvantage compared to other methods. It does not evaluate blood flow volume to the brain directly. However, it has the advantage that it can be used intraoperatively. The "critical point" is a 50% attenuation of the somatosensory-evoked cortical potential in relation to the preoperative examination. Finally, stump pressure measurements can be taken during angiography to determine the pressure on the distal side of the balloon when it is occluded. The critical point is a measurement of <50 mm Hg. There is significant individual variability with this measurement, as it is affected by systemic blood pressure.

Intraoperatively, patients with obvious involvement of the wall of the carotid artery whose preoperative evaluation indicates intolerance to carotid ligation should have the artery reconstructed. Saphenous vein grafts are preferred over prosthetic grafts for reconstruction, and if the skin has been heavily radiated or a portion of skin over the carotid artery is resected, an appropriate flap should be used to cover the graft. There is still considerable debate regarding the routine use of intraoperative shunts, and to date, there has not been a prospective study to prove their usefulness. However, shunting is clearly indicated when there is angiographic evidence of inadequate flow through the circle of Willis.

Postoperatively, delayed strokes can occur in as many as 25% of patients

who have undergone carotid artery resection without reconstruction, even if they “passed” the balloon occlusion test.[150] Flow from the contralateral side through the circle of Willis prevents a stroke initially. However, the resection creates an arterial stump that begins at the takeoff of the middle cerebral artery and continues down to the level of the resection. This can be a site for thrombus formation, which can then propagate up into the circle of Willis. Alternatively, the thrombus may produce emboli that can travel into the distribution of the middle cerebral artery. Although these mechanisms have not been conclusively proven, many surgeons advocate the use of heparin postoperatively to prevent delayed strokes following resection of the internal carotid artery. Recommended doses range from 5,000 units subcutaneously twice a day to full therapeutic anticoagulation.[151] The benefit of anticoagulation has not been demonstrated in a prospective controlled study.

Primary Cancer Treated with Radiation with or without Chemotherapy

The management of patients treated with “organ preservation” strategies using radiation and, more recently, combinations of radiation and chemotherapy, who present with clinically obvious lymph node metastases, particularly those with advanced metastasis to the neck (N2/N3) is evolving and remains somewhat controversial.

The first controversy is whether or not a planned neck dissection (PND) should be performed, irrespective of the response of the cancer in the neck to the treatment with radiation or chemoradiation. Some clinicians argue that a neck dissection should be carried out as part of the treatment plan, irrespective of the response of the cancer in the neck, because the clinical and pathologic responses of the tumor in the neck correlate poorly with each other. In a study by Brizel et al.,[152] a planned neck dissection appeared to confer a disease-free survival and overall survival advantage in patients with N2/N3 disease undergoing chemoradiation and had acceptably low morbidity. This was a retrospective study of a cohort of 108 patients with advanced squamous carcinoma of the head and neck, who presented with lymph node metastasis and were treated with hyperfractionated radiotherapy and concurrent cisplatinum and 5-fluorouracil. A “modified neck dissection” was performed in 65 patients, whereas 29 patients did not undergo neck dissection because of “physician and/or patient preference.” The 4-year

disease-free survival was 70% for patients with N1 disease, irrespective of the clinical response or whether a neck dissection was performed. For patients with N2/N3 disease who had a complete clinical response to chemoradiation, the 4-year disease-free survival rate was 75% for those who had a neck dissection and 53% for those who did not. This difference was not statistically significant ($p = 0.08$). However, the 4-year overall survival rate was significantly better (77% vs. 50%) for the group treated with neck dissection ($p = 0.04$). These authors and others have suggested that a planned neck dissection be considered for all patients with N2 and N3 disease.[152,153]

On the other hand, some clinicians argue that it is not necessary to perform a “planned” neck dissection when the cancer in the neck undergoes a complete response to the treatment.[154,155] This position is based on the observation that less than a third of the patients with clinically positive nodes before therapy have histologic evidence of metastases at neck dissection,[156] even when there is residual clinical or radiologic “adenopathy” in the neck after completion of (chemo)radiation.[157,158] Furthermore, when the cancer in the neck undergoes a complete response to the treatment, the probability of an isolated recurrence in the neck is low (0% to 11%); therefore, the patients may simply be observed.[154,159–161]

The controversy over whether or not a PND is needed is in large measure due to the inability to determine, preoperatively, when a complete clinical response is associated with the presence or absence of viable tumor cells. PET scanning has been found useful in identifying the subset of patients who need a neck dissection, because this imaging modality has been shown to be more accurate than others in the evaluation of patients following treatment.[162] However, the timing of posttreatment PET scanning appears to be important. In a series of 12 patients studied prospectively by Rogers et al.,[163] a positive PET scan 1 month after radiation therapy accurately indicated the presence of residual disease in all cases; however, a negative PET scan indicated absence of disease in only 14% of the cases. Other studies have also shown that a PET scan obtained 1 month after completion of treatment with radiation was inaccurate in predicting the presence of residual cancer.[164] In contrast, a PET scan done 12 weeks after completion of treatment with radiation or chemoradiation may be more useful. Porceddu et al.[165] evaluated the utility of PET imaging in 39 patients with N+ neck who achieved a complete response at the primary site but had a residual mass in the neck, 8 weeks or

more after definitive (chemo)radiotherapy. The PET scan was performed at a median of 12 weeks (range 8 to 32 weeks) after treatment. Interestingly, the PET scan showed no metabolic activity in the residual mass in 32 patients. Five of these patients had a neck dissection and were all pathologically negative. The remaining 27 patients were observed for a median of 34 months (range 16 to 86 months), and only one of them had a locoregional recurrence. Thus, the NPV of PET for viable disease in a residual anatomic abnormality in the neck was 97%. These authors concluded that a neck dissection is not necessary in patients who have achieved a complete response at the primary site but have a residual abnormality in the neck that is PET negative ~12 weeks after treatment and that these patients can be observed safely. Others have reported similar results. Rabalais et al. in a retrospective analysis of 52 patients treated with CRT found that 10 (19.2%) had a positive PET scan an average 11.8 weeks after completion of treatment.[166] Three of the 10 underwent neck dissection of which 2 partial responders had residual disease and the 1 complete responder did not. The remaining 7 (70%) patients were observed only. One of these patients was shown to have residual cancer on FNA but was not a surgical candidate for neck dissection and another had cancer in the neck in addition to persistent cancer at the primary site. Of the five remaining patients with positive PET/CT results who did not undergo PND, all five had gradual resolution of the cancer on serial PET/CT scans with no failures in the neck. Of the 42 (81%) that had a negative posttreatment PET finding, 2 underwent neck dissection for palpable lymphadenopathy and 3 had neck dissections as a component of salvage surgery for the primary cancer. None of the five neck dissection specimens demonstrated residual cancer. There were no isolated recurrences in the neck in the remaining 37 patients (average follow-up 60.4 weeks). Recently, Corry et al.[167] reviewed their experience with N2/N3 disease following CRT in 102 patients. Of the 28 patients in whom there was a CR within the primary and a PR in the neck, 11 patients demonstrated resolution of their adenopathy with continued observation, 1 was diagnosed with metastatic cancer prior to any further therapy and 16 patients had a neck dissection of which 9/16 (65%) were pathologically negative. In another study, patients with a clinical complete response to chemoradiation who were observed rather than having a neck dissection demonstrated a regional failure rate of 3% to 8%, and if negative PET imaging was included as part of the definition of a complete response, the regional failure rate decreased to 0% to

3%.[168] Thus, it appears from this information that observation with a PET/CT obtained at least 12 weeks after completion of chemoradiation is a reasonable alternative to a "routine" planned neck dissection.[168]

The second dilemma regarding "planned" neck dissections is the extent of the operation. Traditionally, surgeons performed comprehensive neck dissections (levels I to V) with or without preservation of nonlymphatic structures.[169] Recently, however, surgeons have reported performing SNDs with recurrence rates below 4%.[170] Robbins et al. performed 33 selective neck dissections in patients treated with targeted intra-arterial high-dose cisplatin infusions combined with radiation therapy (RADPLAT).[160,170] There was only one recurrence in the neck. Stenson et al.[171] reported the results in 69 patients who had planned neck dissections after various concomitant chemoradiation protocols. The majority of them (56/69) underwent a selective neck dissection, and only one patient had a recurrence in the neck. These studies suggest that selective neck dissection may be an appropriate option for some patients with an N+ neck who are treated with organ preservation regimens.

Robbins et al.[172] in 2005 reported the results of 106 neck dissections performed in 84 patients with advanced N stage cancer (N2/N3) that were treated with the RADPLAT protocol. Fourteen neck dissections were radical or modified radical, 81 were selective and 11 were dissections of levels II and III and were labeled as "super selective neck dissections" (SSND). Interestingly, there were no recurrences in the neck in the group that underwent SSND. The authors outlined the indications for the different types of neck dissection as follows: in general, a radical or modified RND was performed in patients in whom the residual lymphadenopathy involved multiple levels, a selective neck dissection was performed when the residual cancer was confined to two levels involving the lymph node groups at greatest risk, and an SSND was performed when the residual lymphadenopathy was confined to one level.

Vasan et al., at the University of Oklahoma, investigated the feasibility of performing a "single-level dissection." To that end, they studied a cohort of 51 patients, treated between January 1999 and March 2005, who underwent a total of 55 "planned" neck dissections for clinically or radiologically apparent residual cancer in the neck, after definitive treatment of the primary tumor

and neck with radiation therapy alone or with chemotherapy.[157] The primary cancer was in the tonsil in 20 (39%) patients, the base of the tongue in 12 (23%), the supraglottic larynx in 10 (20%), the hypopharynx in 4 (8%), the faucial arch in 3 (6%), and “unknown” in 2 (4%). The neck was staged N1 in 19 (38%) patients, N2A in 8 (16%), N2B in 10 (20%), N2C in 6 (12%), and N3 in 7 (14%). All patients were treated with radiation therapy with curative intent. The mean radiation dose was 7,077 cGy and 5,814 cGy to the primary cancer and neck, respectively. Twelve patients also received chemotherapy. The neck dissections performed included lymph node levels II to IV in 32 (58%) of the cases, II to III in 16 (29%), I to IV in 4 (7.1%), and one each of I to IV, II to V, and II only. In 19 dissections (34%), nonlymphatic structures were removed, including the IJV (19/34%), a portion or all of the SCM (14/25%), the digastric (5/9%), and the XI cranial nerve (4/7%). Interestingly, Robbins et al.[160,170] also reported the need to remove one or more of these nonlymphatic structures in 24% of “planned” selective neck dissections. The pathologists found histologically “viable-looking” cancer in one or more lymph nodes in 15 of the 55 neck dissection specimens; thus, the yield of histologically positive nodes was 27.2%. In the analysis of the distribution of the positive nodes, five patients had clinical or radiologic evidence of metastases of one or more nodes in level II only; in all of them (5/5), histologically positive lymph nodes were found only in level II. Eight patients had clinical/radiologic evidence of metastases in one or more nodes in levels II and III (one patient also had a node in level V); histologically positive nodes were found in level II in one instance, in level III in four, and in levels II, III, and IV in three. Two patients had clinically/radiologically positive nodes in levels I and II; histologically positive nodes were found in levels I and II in one of them and in levels I and III in the other. Over a mean follow-up time of 25.9 months, there were only two recurrences in the neck (4%).

These findings confirm the effectiveness of selective neck dissection in the management of residual cancer in the neck. In addition, they suggest that it may be feasible to perform a single-level dissection in patients whose cancer is confined to level II nodes, before, during, and after treatment with radiation with or without chemotherapy. Boyd et al.[173] noted a predictable pattern of residual metastases following irradiation and suggested that a lateral (II to IV) neck dissection may be appropriate in the majority of

patients. In this study of nine positive specimens, six revealed malignant cells in a single nodal echelon. Obviously, such an approach must be investigated further in prospective studies.

More recently, investigators have used CT scans of the neck following chemoradiation to determine the extent of neck dissection. Goguen et al.[174] and Yeung et al.[175] noted the NPV for CT for the posttreatment neck was 95%. They noted that an SND or superselective neck dissection guided by posttreatment CT would have captured all residual cancer in 95% and 93% of the cases, respectively.

SEQUELAE OF NECK DISSECTION

The most notable sequelae observed in patients who have undergone a RND are related to removal of the SAN. The resulting denervation of the trapezius muscle, one of the most important shoulder abductors, causes destabilization of the scapula with progressive flaring at the vertebral border, drooping, and lateral and anterior rotation. The loss of trapezius function decreases the patient's ability to abduct the shoulder above 90 degrees at the shoulder. These physical changes result in the recognized shoulder syndrome of pain, weakness, and deformity of the shoulder girdle commonly associated with the RND. It should also be noted that preserving the cervical plexus contributions to the SAN may not decrease shoulder morbidity significantly.[176] Furthermore, shoulder disability after neck dissection results not only from the SAN dysfunction but also from secondary glenohumeral stiffness caused by weakness of the scapulohumeral girdle muscles and postoperative immobility.

A number of studies have demonstrated that when compared with the RND, neck dissections that preserve the SAN are associated with less shoulder pain,[177] better shoulder function and overall quality of life.[5,90–92,178,179] However, these studies also provide evidence that even procedures that involve minimal dissection of the SAN can result in shoulder dysfunction. Although this dysfunction is often reversible, it behooves the surgeon to make every effort to avoid undue trauma to the nerve, particularly stretching, during any neck dissection in which the nerve is preserved. In addition, every patient who undergoes neck dissection must be questioned about the function of the shoulder and must be evaluated by a physical

therapist early in the postoperative period. If any deficit is detected, the patient should be properly counseled and coached to ensure proper rehabilitation of the shoulder. Physical therapy aimed to early recovery of passive motion and to avoid the occurrence of joint fibrosis has been shown to be beneficial.[180] It has also been suggested that progressive resistance exercise training may be a useful adjunct to standard physical therapy.[181] It should be kept in mind, as mentioned earlier, that shoulder pain after neck dissection may not be the result of dysfunction of the SAN. Consequently, if a patient experiences shoulder pain after neck dissection, the trapezius muscle and active bilateral abduction of the shoulder should be examined to determine if the SAN is involved.[93]

COMPLICATIONS OF NECK DISSECTION

In addition to the medical complications that can occur after any surgical procedure in the head and neck region, several surgical complications can be related solely or in part to neck dissection.

Infection

Following clean neck dissections, those in which the upper aerodigestive tract is not entered, wound infections are uncommon. Interestingly, however, a recent prospective study, designed to evaluate the effects of a prophylactic antibiotic regimen (ampicillin–sulbactam for 24 hours) on the incidence of infection after clean neck dissection, showed that the infection rate in patients that were treated with the antibiotic was 1.7% compared to a significantly higher rate (13.3%) among patients who did not receive antibiotic (p = 0.02).[182]

Chylous Fistula

The reported incidence of chyle fistula following neck dissection varies between 1% and 2.5%. In most patients who develop a postoperative chylous fistula, a chylous leakage is identified and apparently controlled intraoperatively.[183] Given these observations, it behooves the surgeon to avoid injury to the thoracic duct proper and to also to ligate or clip any

visualized or potential lymphatic tributaries in the area of the thoracic duct, which may be accomplished with relative ease if the operative field is kept bloodless when dissecting in this area of the neck. Furthermore, as soon as the dissection of this area is completed and again before closing the wound, the area is observed for 20 or 30 seconds while the anesthesiologist increases the intrathoracic pressure.

Even the smallest leak of chylous drainage must be pursued seriously until it is no longer leaking. Direct clamping and ligating may be difficult and sometimes counterproductive as a result of the fragility of the lymphatic vessels and the surrounding adipose tissue. Hemoclips are ideal to control a source of leakage that is clearly visualized. Otherwise, it is preferable to use suture ligatures with pliable material, such as 5-0 silk, that are tied over a piece of hemostatic sponge to avoid tearing. In the immediate postoperative period, serum and drainage levels of triglycerides and cholesterol obtained on the first postoperative day may be useful parameters to predict early the occurrence of a chyle fistula.[184]

Management of a chyle leak noted postoperatively depends on the time of onset of the leak, on the amount of chyle drainage in a 24-hour period, and on the presence or absence of accumulation of chyle under the skin flaps.[183,185] When the daily output of chyle exceeds 600 mL or 200 to 300 mL/day for 3 days, especially when the chyle fistula becomes apparent immediately after surgery, conservative closed wound management is unlikely to succeed.[186] In such cases, it is preferable to explore the wound early, before the tissues exposed to the chyle become markedly inflamed and before the fibrinous material that coats these tissues becomes adherent, obscuring and jeopardizing important nearby structures such as the phrenic and the vagus nerves. Surgical exploration is also warranted when chyle accumulates under the skin flaps either because of inadequate drain size or because of the volume or consistency of the chyle causes partial or complete obstruction of the drains.

On the other hand, chylous fistulae that become apparent later in the postoperative period, after enteral feedings are resumed, or those that drain <200 to 300 mL of chyle per day, are initially managed conservatively with closed wound drainage, pressure dressings (which are cumbersome to secure in this area of the neck), repeated aspirations, and diet modifications aimed at decreasing chyle drainage while maintaining nutritional support. Usually,

nutrition can be provided enterally using elemental diets supplemented with medium-chain triglycerides, which are absorbed directly into the portal circulation bypassing the lymphatic system. In some patients, parenteral nutrition may be necessary.[187] If these measures fail, the neck is surgically explored and the leak is identified and dealt with appropriately. Sometimes, this intervention is unsuccessful and the leak persists. The use of fibrin glue and a clavicular periosteal flap may be useful to control the leak in such cases.[188] Percutaneous lymphangiography-guided cannulation and embolization of the thoracic duct is an effective minimally invasive alternative to open surgical intervention.[189] Success with this technique has been reported in as many as 45% to 70% of the cases.[186] In a recent report, Nyquist et al. described a case in which a chylous fistula stopped draining 24 hours after the administration of octreotide (100 μm given subcutaneously three times a day). These authors postulate that the effect of octreotide on chylous fistulae may be due to its ability to reduce gastrointestinal and pancreatic secretions, decrease hepatic venous pressure, and reduce splanchnic blood flow, which may decrease thoracic duct flow and relative concentration of triglycerides.[190]

Ipsilateral chylothorax can occur following neck dissection. Bilateral chylothorax as a complication of neck dissection is extremely rare, but it is potentially serious and sometimes fatal.[191,192]

Facial or Cerebral Edema

Synchronous bilateral RNDs, in which both IJVs are ligated, can result in the development of facial edema, cerebral edema, or both. The facial edema sometimes can be dramatically severe. It appears to be a mechanical problem of venous drainage, which resolves to a variable extent with time as collateral circulation is established. It appears to be more common and more severe in patients who had previous radiation to the head and neck and in those patients in whom the resection includes large segments of the lateral and posterior pharyngeal walls. We have been able to prevent massive facial edema by preserving at least one external jugular vein whenever a bilateral RND is anticipated. The external jugular usually is separated from the tumor in the neck by the SCM and can be dissected free between the tail of the parotid and the subclavian vein. Others have reconstructed one internal jugular using various techniques including vein with saphenous vein grafts or by using a

segment of one of the resected jugular veins, distal to the site of tumor involvement.[193,194] The development of cerebral edema may be at the root of the impaired neurologic function and even coma that can occur after bilateral RND. Following neck dissection, a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occurs in 8% to 30% of patients. This is a disorder in which release of antidiuretic hormone is independent of plasma osmolarity, resulting in fluid retention and development of dilutional hyponatremia. It occurs significantly more often in patients who have history of smoking, and it has been noted to resolve within 72 hours.[195] It is commonly believed that synchronous, bilateral RND causes the SIADH, presumably as a result of increased intracranial pressure. This belief is based mainly on the results of an experimental study published in 1978 in which occlusion of the superior vena cava in dogs resulted in increased intracranial pressure and SIADH. Using an animal model that more closely resembles the clinical condition of bilateral RND, Khafif et al. found that bilateral synchronous IJV ligation and bilateral RNDs did not result in SIADH in dogs.[196] As these results contradict a commonly held belief in clinical practice, a prospective evaluation of the physiologic changes after bilateral RNDs is warranted. Nevertheless, it is possible that an expansion of extracellular fluids and dilutional hyponatremia that occurs in some patients after neck dissection could aggravate cerebral edema, creating a vicious cycle. In practice, this behooves the surgeon and the anesthesiologist to curtail the administration of fluids during and after bilateral RNDs. Furthermore, perioperative management of fluid and electrolytes in these cases should not be guided solely by the patient's urine output but also by monitoring central venous pressure, cardiac output, and serum and urine osmolarity.

Carotid Artery Rupture

The most feared and most commonly lethal complication after neck surgery is exposure and rupture of the carotid artery, the so-called carotid blowout syndrome (CBS). Therefore, every effort must be made to prevent it. Prevention of CBS begins with an understanding and avoidance of the circumstances that predispose to CBS; these include:

1. Previous treatment with radiation or chemoradiation, malnutrition, and diabetes impair healing capacity and compromise vascular supply that

may lead to wound breakdown, skin flap necroses, and fistula formation.

2. Neck incisions with trifurcations over the carotid: small areas of necrosis of the tips of flaps at the trifurcation can result in exposure of the carotid. If the skin incisions are designed properly, the carotid seldom becomes exposed in the absence of a salivary fistula.

Faced with any of these risk factors, the surgeon must (1) use flawless surgical technique in the closure of oral and pharyngeal defects, (2) perioperative antibiotics, and (3) use free and pedicled vascularized flaps, which provide skin for closure of mucosal defects and muscle that can protect the carotid. These measures have rendered obsolete the use of “protective” measures such as dermal grafts, levator scapulae muscle flaps, and controlled pharyngostomes.

Fortunately, CBS has become less frequent; however, its frequency may increase again as more salvage procedures are done in patients whose tumors fail to respond to chemoradiation regimens. Therefore, it is essential for all head and neck surgeon to be familiar with presentation and current management of CBS.

A patient may present at different stages of CBS that range from exposure of the carotid artery to hemorrhage from the carotid artery system and management varies accordingly.

Stage I or threatened CBS, when exposure of the carotid artery is found on clinical examination or imaging studies (i.e., air surrounding the vessel, adjacent abscess, or tumor associated with a fistula or areas of arterial wall disruption, found on vascular imaging studies). At this stage, the patient may be asymptomatic.

Stage II or impending blowout, when bleeding episodes occur that resolve temporarily with pressure and wound packing. In many cases, these are self-limiting, single incidents that may cause little suspicion to those unaware of the patient’s history and risk factors for CBS. Sentinel bleeding can occur moments to months before hemorrhage.

Whenever the carotid is exposed, it is advisable to take the following precautions:

- Warn and instruct nursing personnel and house staff about the possibility of a carotid rupture, the site of potential rupture, and the steps

to be taken in the event of bleeding.

- Have compatible blood available.
- Keep appropriate surgical instruments at the bedside.

Management of the exposed carotid depends on the likelihood of rupture, based on the length of the exposed segment, the condition of the surrounding tissues, and the size of the oropharyngocutaneous fistula. Large cutaneous defects or large high-output fistulae in previously radiated patients are not likely to heal by secondary intention in a timely manner. The likelihood of rupture of the carotid in these conditions is extremely high. Therefore, an attempt should be made to repair the defect and to cover the carotid using well-vascularized tissue early, before the vessel has been irreversibly damaged.

Identification and appropriate management of the early stages of CBS are crucial, as these patients have a lower complication rate than do those who wait until hemorrhage develops.

Stage III or hemorrhage from the carotid system. This can be rapidly fatal especially when it occurs outside the hospital setting. Bleeding can occur externally through a neck wound or “internally” into the pharynx/mouth. In the latter case, the possibility exists for airway compromise. When a carotid rupture occurs, it is usually possible to stop the bleeding with manual pressure while blood and fluids are given to restore and maintain the patient’s blood pressure. Often, in emergency situations, medical staff place multiple dressings over the wound, which will not apply focused pressure over the bleeding site, and the patient may continue to exsanguinate around them. It is more effective to place a gloved finger for pressure to temporarily control the bleeding until definitive treatment is undertaken. Blood pressure must be addressed aggressively with proper resuscitation. Only then is the patient taken to surgery or the radiology suite, because the risk of morbidity with ligation increases significantly in the setting of hypotension, which is the greatest predictor of a poor outcome in the acute treatment of CBS. Attempts to repair the area of rupture are futile. Introducing Fogarty catheters through the area of rupture help control the bleeding temporarily while the artery is exposed and ligated proximally and distally to the area of rupture.

Endovascular embolization—whether it be with balloons, coils, or other

materials—is more precise than ligation, as it targets the exact location of the arterial defect. It also decreases the hospital stay and causes less of the collateral morbidity that is sometimes associated with emergent open ligation procedures, such as injury of cranial nerves or ligation of the incorrect trunk or branch of the carotid system. Endovascular embolization also has the ability to help predict cerebrovascular complications with temporary balloon occlusion and collateral cerebral blood flow analysis. Carotid artery embolization is associated with 15% to 20% long-term neurologic morbidity rate and a much lower incidence of associated mortality.

More recently, constructive endovascular management of CBS became available for patients who have risk factors for neurologic sequelae after embolization. Constructive methods using intravascular stents to control vascular wall instability while allowing adequate cerebral perfusion. Some indications used for arterial stenting include an incomplete circle of Willis, significant contralateral carotid artery atherosclerosis or narrowing, inability to perform balloon occlusion tests (proximal atherosclerotic stenosis or unstable clinical scenario), and failure to tolerate balloon test occlusion on either clinical or cerebral blood flow criteria (decrease of cerebral blood flow of more than 20%).

Regardless of the treatment used, anticoagulation therapy may be required to prevent thrombosis distal to the ligation or endovascular occlusion site or to prevent stent thrombosis. Patients with an exposed carotid artery require wound management with flap placement to cover and protect these vessels.

Although endovascular treatment within the carotid system can have a significant risk of mortality and neurologic morbidity, it has become the treatment of choice for CBS.

Jugular Vein “Blowout”

This complication is seen more often because the IJV is preserved more frequently during neck dissection. Rupture of the jugular vein should be considered in patients undergoing primary excision of cancer with a modified RND complicated by a pharyngocutaneous fistula. In a recent study of six patients who experienced rupture of the IJV, Cleland-Zamudio et al.[191] found that patients who have a complete circumferential dissection of the IJV low in

the neck and go on to have fistulas develop may be more prone to this complication.[197] Typically, bleeding occurs repeatedly. Treatment consists of surgical exploration and ligation of the jugular vein above and below the level of rupture.

Jugular Vein Thrombosis

Preservation of the IJV during neck dissection does not ensure its patency after surgery, particularly when radiation therapy is also used. Cotter et al.[198] used preoperative and postoperative CT or MRI on 69 patients undergoing 79 vein-sparing neck dissections. Sixty-eight veins (86%) were patent postoperatively. Capiello et al. studied the patency of the IJV following selective lateral neck dissection in a cohort of 34 patients. A preoperative baseline study of vein patency and flow by US was obtained followed by postoperative evaluations at 1 week, 1 month, and 3 months. At 1 week postoperatively, 50% of the IJVs did not present any alteration in patency, 46% had reduced flow, and 4% showed absent flow. However, at 3 months, none of the patients showed evidence of IJV occlusion. Postoperative radiotherapy did not have a statistically significant impact on IJV patency ($p = 0.09$).[199]

A recent report describes the rate of complications after planned posttreatment neck dissections in patients enrolled in organ preservation protocols. The authors conclude that the rate is similar to that previously reported for neck dissections (37%) and that the rate increases when higher preoperative radiation therapy doses are used.[200]

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19 Thyroid Cancer

Jennifer R. Cracchiolo Ashok R. Shaha

The incidence of thyroid cancer is rapidly rising in the United States and around the world.[1] This is largely related to the routine use of ultrasound and imaging studies including CT scan, MRI, and PET scan in the evaluation of other conditions, which leads to the early identifications of thyroid nodules many of which after further analysis prove to be thyroid cancer. The incidence of thyroid cancer has almost quadrupled in the United States in the last quarter of a century from ~8,000 cases per year in 1975 to the current incidence of 66,000 new thyroid cancers per annum. A much steeper rise in incidence has been seen in Korea where ultrasound of the neck is performed in a routine health check. The vast majority of these incidentally identified thyroid cancers are papillary carcinomas <2 cm in size, for which the 5-year survival exceeds 99.5%. However, the finding of thyroid cancer in each patient leads to intense concern about the diagnosis of cancer, often leading to aggressive treatment that is costly and, at times, morbid.

There is a current debate as to whether relatively more aggressive treatment will make a difference in long-term outcome, given that the outcome in patients with small papillary carcinomas is excellent. Thus, questions remain as to whether the routine use of total thyroidectomy with such patients is more likely to lead to improvements in survival that would justify the risk of laryngeal nerve palsy and temporary or permanent hypoparathyroidism. There is now a considerable interest both in Japan and in the United States to conduct observation studies on patients with microcarcinoma similar to prostate cancer to determine whether treatment of thyroid cancer is needed in all patients. Given the vast numbers of patients diagnosed and treated for thyroid cancer each year, the prognostic factors and risk group analysis are extremely well defined for patients with thyroid cancer that helps with the selection of how aggressively patients should be treated and which patients could potentially be observed closely rather than treated.

The majority of thyroid cancers are papillary carcinoma with follicular, Hurthle cell, anaplastic, and medullary carcinoma representing the remaining histologies that are most commonly seen (Fig. 19.1). Significant advances in the molecular biology of thyroid cancer have contributed to the way in which thyroid cancer is understood, diagnosed, and managed, as molecular testing now aids in predicting malignancy and prognosis in cytopathology samples. In addition, three drugs recently approved by the FDA for the treatment of advanced thyroid cancer are currently being used. With all of these new technologic developments currently available, it is important to continue to adhere to the principles of management of patients with thyroid cancer to avoid treatment-related complications both medical and surgical.

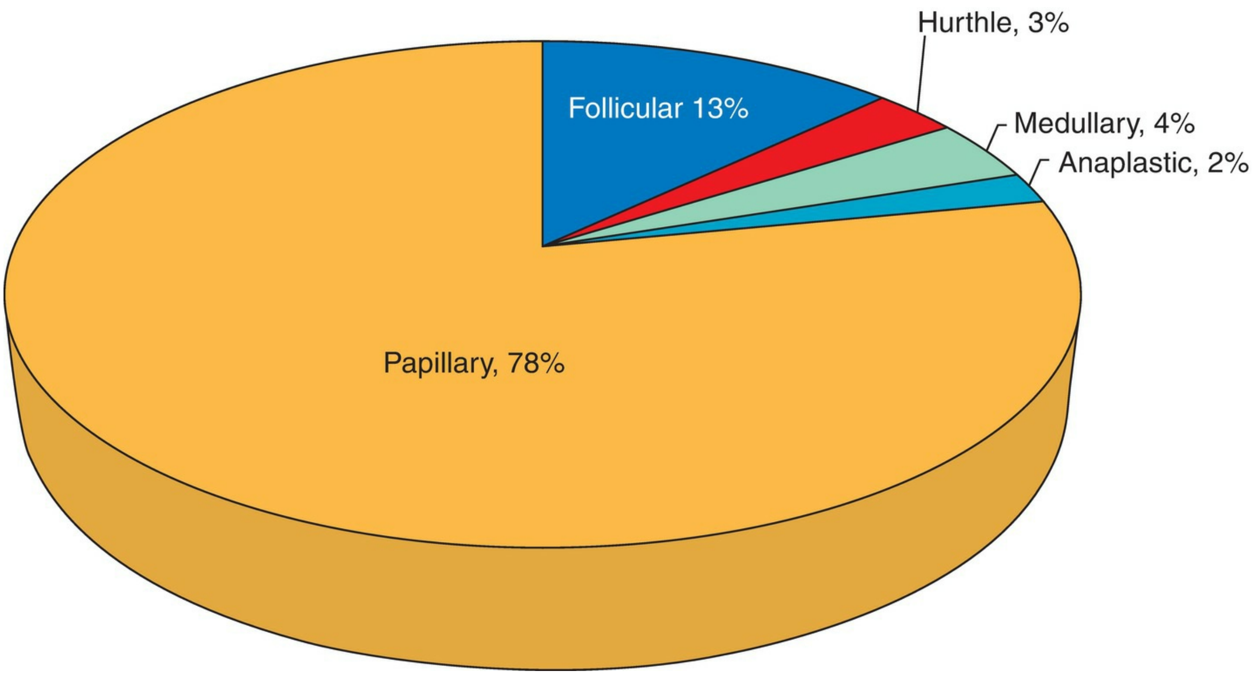

Figure 19.1. Histologic distribution of thyroid tumors.

In this chapter, we will discuss the current understanding of thyroid cancer, pathology, prognostic factors and risk group analysis, available treatments, and overall outcomes. Current recommendations for evaluation, treatment, and surveillance are based on the wide experience of practitioners, investigators, and organizations such as the American Thyroid Association (ATA) and have led to publication of guidelines for the management of thyroid cancer first in 2006 and most recently in 2015.

THYROID CANCER: A UNIQUE HUMAN NEOPLASM

Thyroid cancer is a unique human neoplasm as the overall biologic behavior of thyroid cancer is characterized by slow-growing tumors with progression of disease over many years. Furthermore, this is the only human neoplasm where age is included in the staging system (Tables 19.1 and 19.2). In fact, here is no stage III or IV thyroid cancer in patients below the age of 45, which reflects the excellent outcome of these patients even in the setting of distant metastases. Age is an important prognostic factor, and even though age 45 is used as the general threshold in the staging system, it appears that the better age threshold is at 55.[2] The presence of microscopic or “laboratory cancer” has very little clinical significance. It is not uncommon to find laboratory microscopic cancer in a thyroid gland removed for other medical issues. Such microscopic papillary cancers have an excellent prognosis and do not have any implication in the long-term outcome and do not require additional treatment. The presence of nodal metastasis in thyroid cancer is fairly common and is seen in almost 60% to 80% of younger individuals diagnosed with the disease. It has no major bearing in the overall outcome except in selective aggressive thyroid cancers or in older individuals.

Table 19.1 AJCC Staging of Thyroid Cancer

Definition of TNM	
Category	**Definition**
Primary tumor (T)[a]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in its greatest dimension, limited to the thyroid
T2	Tumor more than 2 cm, but not more than 4 cm in its greatest dimension, limited to the thyroid
T3	Tumor more than 4 cm in its greatest dimension limited to the thyroid or any tumor with minimal extrathyroidal extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a[b]	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b[b]	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Regional lymph nodes (N)[c]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to level VI (pretracheal, paratracheal. and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	Mo distant metastasis
M1	Distant metastasis

[a]All categories may be subdivided: (I) solitary tumor, (ii) multifocal tumor (the largest determines the classification).

[b]All anaplastic carcinoma are considered T4 tumors: T4a—intrathyroidal anaplastic carcinoma (surgically resectable); T4b—extrathyroidal anaplastic carcinoma (surgically unresectable).

[c]Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Table 19.2 AJCC Staging of Thyroid Cancer

Staging	T	N	M
Papillary or follicular under 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Papillary or follicular 45 years and older			
Stage 1	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Medullary carcinoma			
Stage 1	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	TI	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Anaplastic carcinoma[a]			
Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

[a]Any anaplastic carcinomas are considered Stage IV.Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

An understanding of the histologic variations of thyroid carcinoma such as tall cell insular or poorly differentiated tumors and aggressive features is critical in the selection of treatment for patients in order to assure that they have the best possible outcome. In addition, these factors are important for the selection of adjuvant treatment and follow-up testing. The number of mitoses seen per high-power field on histologic examination is also important as a major prognostic feature, as are the findings of extrathyroidal extension and invasion of surrounding structures. It is critically important that the operating surgeon appreciate these clinical features and perform adequate and appropriate surgery including resection of the surrounding involved structures to achieve a complete resection in order to avoid future locoregional recurrence.

Despite all that is known about the biologic behavior of differentiated thyroid cancer, there are several controversies that remain regarding its management. One major area of controversy has been a subject of debate in national and international conferences and the literature abounds with publications describing the extent of thyroidectomy and whether treatment with thyroid lobectomy versus total thyroidectomy is the most appropriate way to manage patients with early-stage differentiated cancer. Two additional areas of controversy are (1) the use of radioactive iodine ablation in patients with low-risk thyroid cancer and (2) whether prophylactic central compartment dissection should be performed in patients with low-risk thyroid cancers. These controversies generate considerable debate, and this has been reflected in the evolution of the ATA guidelines for thyroid cancer treatment from 2006 to 2015.

EPIDEMIOLOGY

The National Cancer Institute has reported that 62,980 people will be diagnosed with thyroid cancer, and 1,890 people will die of this disease in the United States this year. The risk for thyroid cancer is three times more

prevalent in women than men and more common in Caucasians. The probability of being diagnosed with thyroid cancer peaks between 35 and 44 years of age. Although the diagnosis of thyroid cancer affects young patients, the percent of thyroid cancer deaths is highest among older patients with the median age of death being 73 years. Rates for new thyroid cancer cases have been rising on average 5.5% each year over the last 10 years. This increase in incidence is not isolated to the United States as the rise in thyroid cancer has been observed over the last three decades all over the world. The exception to this trend is in Africa, where detection may be insufficient. Importantly, death rates have also been rising on average 0.8% each year over 2002 to 2011.[3] Many have hypothesized on the reasons behind the rising incidence of thyroid cancer, and explanations for the worldwide increase in thyroid cancer incidence are a source of controversy. The recent advances in imaging studies such as ultrasound, CT scan, MRI, and PET scan have identified exceedingly high number of incidental thyroid cancers, which are generally microcarcinomas. This is directly related to the increased usage of ultrasound and other imaging studies of the neck in the evaluation of other conditions including carotid vascular disease, cervical spine problems, and trauma. Many institutions have routine health checks with ultrasound of the neck as well as ultrasound of the breast. This practice of performing routine ultrasound of the neck has led to an exceedingly high incidence of thyroid cancer in South Korea where the incidence has risen almost 15-fold in the last 15 years.[1] Although it is generally accepted that early detection of cancers is generally associated with better outcomes and has led to screening for prostate and breast cancer, the impact of the early identification of papillary microcarcinomas on patient survival remains unclear at this time, and further studies are needed to determine the most appropriate management that will lead to good survival, low morbidity, and appropriate utilization of health care resources.

INCIDENTALLY DIAGNOSED THYROID CANCER

Many thyroid cancers are identified as an incidental finding during the evaluation of other conditions or during screening tests, and these otherwise asymptomatic cancers can therefore be referred to as “incidentalomas.”

Incidentalomas are fairly common in the thyroid gland. This terminology was previously used routinely for adrenal lesions, and it is now commonly used for thyroid nodules found “incidentally” without clinical symptoms or suspicion. Approximately 5% to 10% of individuals have thyroid nodules; however, many of these may remain clinically silent in the lifetime of the individual.

Clinical incidentalomas are commonly noted in routine clinical examination either by a primary care physician or during an ENT examination. Imaging incidentalomas can be divided into ultrasound of the neck, CT scan, MRI, or PET. These are more common when a patient undergoes routine imaging of the neck for other medical problems such as trauma, neck pain, or neurovascular conditions. Once a thyroid nodule has been identified by one of these studies, further evaluation including an ultrasound and needle biopsy may lead to the diagnosis of cancer.

We are seeing more and more incidentalomas related to the use of PET, which raises a suspicion of cancer in the mind of the radiologist and the oncologist. Incidentalomas identified by PET need to be divided into those with diffuse and those with focal uptake. Diffuse uptake is more likely related to nodular hyperplasia and Hashimoto thyroiditis, although the latter condition may also have areas of focal uptake, suggestive of malignancy.

Once a focal incidentaloma is noted on PET, it is important to proceed with ultrasound and based on the findings of the ultrasound consider ultrasound-guided needle biopsy. Katz and Shaha[4] have described their experience and review of PET-associated incidental neoplasms (PAIN) and have noted that the incidence of malignancy in selectively operated patients is ~50%, whereas a large number of these patients have aggressive histology such as tall cell tumor, Hurthle cell tumors, or oncocytic malignant tumors. Figure 19.2 demonstrates a thyroid nodule indecently found by PET scan. In summary, the focal PET hypermetabolic thyroid nodule needs to be further evaluated with ultrasound and possible ultrasound-guided needle biopsy.

Figure 19.2. PAIN (PET-Associated Incidental Neoplasm). Lesions found incidentally on PET scan have a higher rate of malignancy.

ANATOMY

The thyroid gland includes two lateral lobes, connected by a central isthmus. Often, a vestigial remnant of the thyroglossal duct tissue extends as a finger-like projection superiorly from the thyroid isthmus to make up a third, “pyramidal lobe” of the gland. Two ligaments “attach” the thyroid from the cartilaginous airway. The anterior suspensory ligament arises from the anterior aspects of tracheal rings and inserts on the posterior aspect of the thyroid isthmus. Condensation of the thyroid capsule forms the posterior suspensory ligament (ligament of Berry) and connects the posteromedial aspect of the gland to the tracheal rings and cricoid cartilage. In contrast to the avascular plane characteristic of the anterior suspensory ligament, an arterial and venous plexus course through the posterior suspensory ligament and can be a source of bleeding during thyroidectomy.

The arterial and venous supply to the thyroid must be meticulously dissected and ligated during thyroid surgery. Arterial anatomy includes paired superior thyroid arteries arising as the first branch of the external carotid artery and paired inferior thyroid arteries arising from the thyrocervical trunks. An unpaired thyroid ima artery may arise from the innominate artery, carotid artery, or directly off the aortic arch. Attention to hemostasis and keen attention to vascular structures associated with the thyroid gland are important in avoiding postoperative hematoma.

Identification and preservation of the nerves arising from the vagus nerve during thyroid surgery require a thorough knowledge of the anatomy as well as surgical skill. The recurrent laryngeal nerve (RLN) innervates all intrinsic muscles of the larynx except the cricothyroid muscle. The left RLN branches from the vagus nerve and then descends into the chest passing inferior and posterior to the aortic arch. In contrast, the right RLN leaves the vagus nerve at the base of the neck and loops around the subclavian artery. This results in the more lateral location of the right RLN versus the left RLN in the neck as both nerves ascend in tracheoesophageal groove before entering the larynx at the cricothyroid joint (Fig. 19.3). The nerve may be split into multiple branches or into two major branches anterior and posterior. It is the anterior

branch that carries motor fibers and is more functionally important for the mobility of the vocal cord.

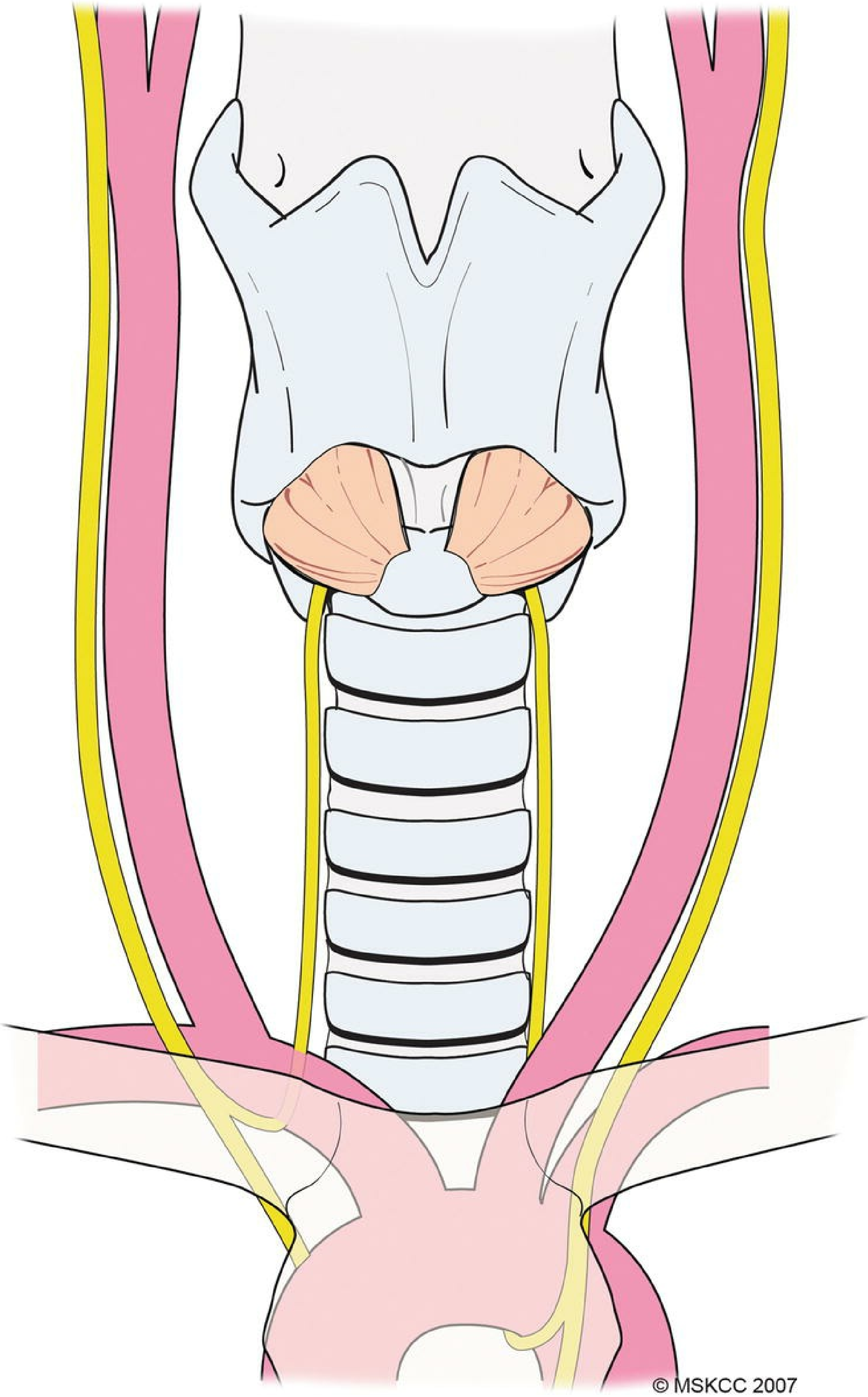

Figure 19.3. The left RLN branches from the vagus nerve and then descends into the chest passing inferior and posterior to the aortic arch. The right RLN leaves the vagus nerve at the base of the neck and loops around the subclavian artery. This results in the more lateral position of the right RLN.

Most of the time, nerve injury is related to thermal injury or traction injury rather than direct transection of the nerve. It is also important to recognize that the entry point of the RLN is a fixed point, and therefore, stretch injury when retracting the thyroid medially during surgery can also occur. The anatomical identification of the tuberculum Zuckerkandl can aid in the identification of the RLN. This anatomic structure is present in majority of the patients with thyroid pathology. It is a small outpouching of the thyroid tissue, which forms a tiny tubercle near the ligament of Berry. Often, the nerve is posterior and slightly medial to the tuberculum Zuckerkandl and is a good landmark for identification of the RLN (Fig. 19.4A and B). Occasionally, the tuberculum of Zuckerkandl may displace the RLN laterally around it, placing the nerve at risk for injury if this variation is not recognized (Fig. 19.4C). The nerve may be intimately adherent to this region, which could also predispose it to injury.

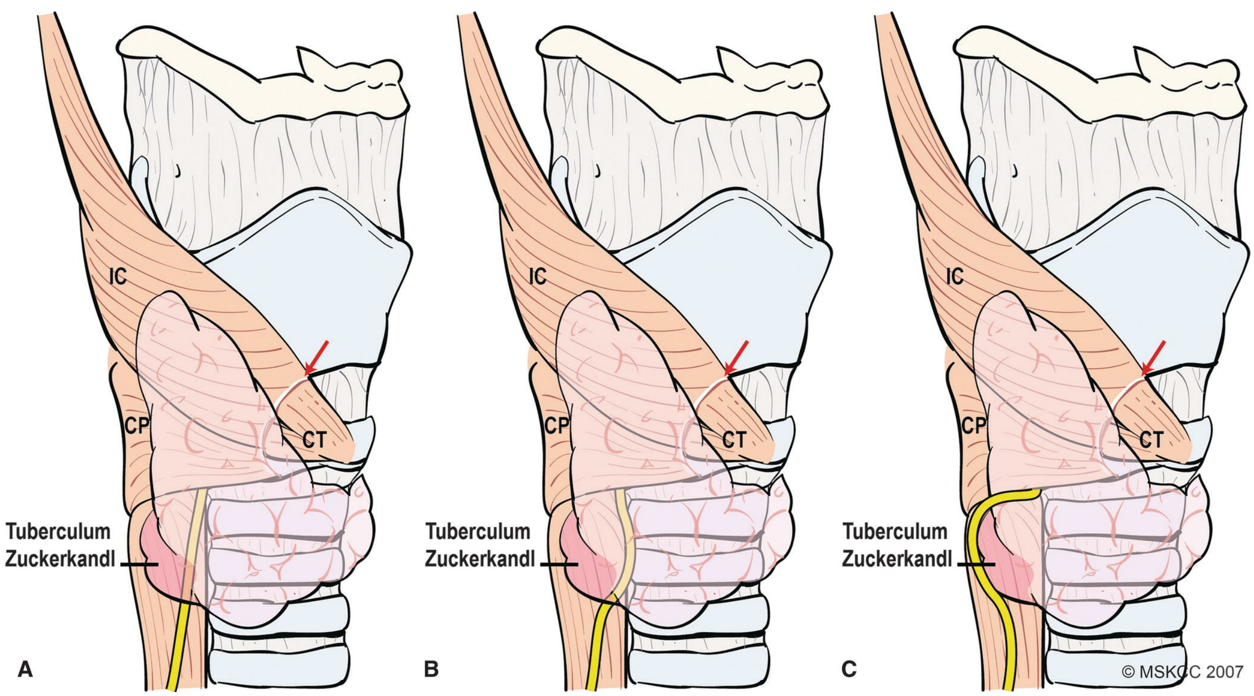

Figure 19.3. A and B: The RLN lies posterior and slightly medial to the tuberculum Zuckerkandl and is a good landmark for identification of the

RLN. **C:** Occasionally, the tuberculum of Zuckerkandl may displace the RLN laterally around it, placing the nerve at risk for injury.

There are three areas where the RLN can be injured. The first is in the tracheoesophageal groove, which is often encountered during the dissection of the lymph nodes in the tracheoesophageal groove. This is the same area where the nerve may be traumatized due to adherence of the lymph nodes or more importantly while dissecting the nerve off the lymph nodes. The nerve may also be injured at the crossing of the inferior thyroid artery. In the majority of the time, the nerve crosses behind the inferior thyroid artery; however, in ~25% of patents, the nerve may be superficial to the inferior thyroid artery where the identification of the nerve may be difficult and inadvertently traumatized. The most common injury to the RLN occurs near the ligament of Berry. The most common reason for injury to the RLN in this region is that small blood vessels travel through the ligament of Berry causing excessive bleeding during surgery, and the nerve injury may occur in an effort to control the bleeding in this region especially when electrocautery is used. Occasionally, the laryngeal nerve may be nonrecurrent, and identification of the nonrecurrent nerve is critical in order to avoid unanticipated injury. As this anatomic variant is associated with an aberrant innominate artery or retroesophageal subclavian artery, a preoperative CT scan revealing these vascular anomalies can raise the surgeon’s vigilance for identification of a nonrecurrent nerve. Generally, the presence of a retroesophageal innominate artery (arteria lusoria) leads to the innominate abnormality of being a nonrecurrent RLN. In such patients, extreme care must be undertaken to evaluate the area between the carotid artery and ligament of Berry to avoid injury to the nonrecurrent nerve. The use of a nerve monitor may be extremely helpful in such patients. Generally, the nonrecurrent nerve is identified either at the ligament of Berry or in the region lateral to the superior pole of the thyroid. Occasionally, the vagus nerve may be medial to the carotid artery, which is also an indication of patient having nonrecurrent RLN.

Another important nerve to identify during thyroid surgery is the external branch of superior laryngeal nerve (EBSLN), which has also been called the “Amelita Galli-Curci,” nerve after the famous Italian opera singer whose career declined after she underwent a thyroidectomy. Although less discussed, injury to the (EBSLN) has been estimated to occur in 0% to 53%

of thyroidectomies.[5,6] The superior laryngeal nerve originates from the vagus nerve just below the jugular foramen. It then divides into an internal and external branch. The EBSLN descends inferiorly to innervate the cricothyroid muscle. Cernea anatomically classified variants of the EBSLN.[7] Type 1 nerves cross >1 cm above the upper border of the thyroid gland. Type 2a nerves cross within 1 cm of the upper border of the thyroid. Type 2b nerves cross below the upper border of the gland. The external branch of the superior laryngeal nerve is at risk for injury during ligation of the superior thyroid vascular pedicle most often in patients with the type 2b variant. Patients with injury to the EBSLN during thyroidectomy will complain of inability to yell or "hit a high note."

The superior parathyroid glands ("deep" parathyroids) are derived from the fourth branchial pouch.

Anatomically, these glands exist "deep" to the RLN anatomically. This relationship can change when retracting the thyroid medially during surgery. Classically, the superior parathyroid glands are described as located 1 cm above the intersection of the RLN and inferior thyroid artery. Inferior parathyroid glands ("superficial" parathyroids) are derived from the third branchial pouch. These glands exist superficial to the RLN and are more variable in location. The thymus is also derived from the third branchial pouch, which is why inferior parathyroids are sometimes located in the anterior mediastinum within the thymus.

EVALUATION OF THE THYROID NODULE

Thyroid nodularity is quite common and has been reported to be detected as a palpable nodule in 4% to 7% of the adult population. When imaging is used to evaluate the thyroid, the incidence of nodules identified increases to >50%.[8] Most clinically detected nodules are benign, and the incidence of occult cancer within the thyroid gland ranges from 4% to 35% in adults in autopsy studies. Strikingly, this number approaches 100% in elderly patients.

Generally, nodules >1 cm should be further evaluated for the presence of cancer. However, there are nodules that do not meet this size criterion that should also be evaluated based on suspicious features. Table 19.3 highlights

these features including suspicious ultrasound (US) findings, associated lymphadenopathy, a history of head and neck irradiation, or a history of thyroid cancer in one or more first-degree relatives. Additionally, nodules found incidentally on PET scan have a risk of malignancy of about 33% and may be more aggressive and therefore should be evaluated even if <1 cm.[9] Importantly, the new version of the ATA guidelines recommend not biopsying lesions under 1 cm given the increased interest in observation as a treatment option for subcentimeter PTCs.

Table 19.3 Indications for FNA of Thyroid Nodules <1 cm
Suspicious US findings
Associated lymphadenopathy
History of head and neck irradiation
History of thyroid cancer in first-degree relatives
18FDG-positive nodules

Adapted from ATA Guidelines 2009 version.

Evaluation of a thyroid nodule should include a full history and physical examination. Risk factors, summarized in Table 19.4, include radiation to the head and neck during childhood for cancer or dermatologic pathology such as acne or dermatitis, exposure to radiation secondary to fallout from nuclear accidents such as occurred in Chernobyl, a family history of thyroid carcinoma, or thyroid cancer syndromes such as Cowden, familial polyposis, or type 2 multiple endocrine neoplasia (MEN 2). A history of rapid growth or hoarseness should raise suspicion for malignancy. Physical examination should include the thyroid gland, lateral cervical lymph nodes, and laryngeal examination.

Table 19.4 Clinical Features of a Malignant Thyroid Nodule

Age—Very Young or Very Old
Sex—Male
History of thyroid cancer syndromes
Hoarseness-vocal cord paralysis
Hard, Fixed Nodule
Rapid Growth
New onset of rapid growth in a longstanding stable nodule
Cervical Metastases
Pulmonary Metastases

In the clinically apparent or incidentally found thyroid nodule, a TSH level should be ordered to differentiate functioning from nonfunctioning nodules. If the TSH is low, then a hyperfunctioning nodule should be considered and a radionuclide thyroid scan can be obtained. Hyperfunctioning nodules rarely harbor malignancy, if one is found that corresponds to the nodule in question, no cytologic evaluation is necessary. In contrast, if the TSH is normal or low, further cytologic evaluation is indicated. Interestingly, high TSH has been associated with a higher risk of malignancy.[10] With biochemical evaluation, radiographic assessment is essential in the evaluation of thyroid nodules. Ultrasound of the thyroid gland and lateral neck provides valuable information. First, is there a nodule that correlates to a palpable or radiographic abnormality? If so, how big is it, where is it located with regard to the strap muscles, RLN, or airway? Is it cystic or solid? Completely cystic nodules have a low likelihood of malignancy.[11] Are there other nodules within the gland? Does the nodule have any suspicious findings? Ultrasound characteristics associated with a higher rate of malignancy include hypoechogenicity, increased intranodular vascularity, irregular infiltrative margins, microcalcifications, an absent halo, and taller than the wider diameter. Findings of isoechogenicity and spongiform appearance are more common in benign nodules.[12] Table 19.5 summarizes ultrasound findings, which are useful in distinguishing benign from malignant lesions. Is there concerning lymphadenopathy? Ultrasound

can also help guide fine-needle aspiration (FNA) in nodules that are nonpalpable, partially cystic, or posteriorly located. FNA is the workhorse for cytologic and molecular assessment of thyroid nodules. Cytologic evaluation is classified by the Bethesda System for Reporting Thyroid Cytopathology[13] (Table 19.6).

Table 19.5 Ultrasound Finding in Thyroid Nodules

Benign Features	Malignant Features
Pure cystic nodule Spongiform appearance Benign nodules	Micro- or Macrocalcifications Marked hypoechogenicity Taller-than-wide shape Spiculated margin

From Moon WJ, et al.; Thyroid Study Group, Korean Society of Neuro- and Head and Neck Radiology. Benign and malignant thyroid nodules: US differentiation—multicenter retrospective study. *Radiology*. 2008;247(3):762–770.

Table 19.6 Bethesda Criteria

Bethesda Criteria	FNA Result	Chance of Malignancy
I	Nondiagnostic or Unsatisfactory	1%–4%
II	Benign	0%–3%
III	Atypia of Undetermined Significance Follicular Lesion of Undetermined Significance	5%–15%
IV	Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15%–30%
V	Suspicious for Malignancy	60%–75%
VI	Malignant	97%–99%

From Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. *Am J*

Clin Pathol. 2009;132(5):658–665.

Molecular testing may provide further information on thyroid nodules including risk of malignancy and prognosis. Afirma is a molecular test used in indeterminate nodules by FNA (Bethesda III and IV) as a “rule out test.” This test takes into account mRNA expression levels in a 164-gene panel. This Gene Expression Classifier (GEC) provides results that are either benign (<6%) or suspicious (40% chance of malignancy) with a negative predictive value of 94%.[14] The majority of the clinicians will use this information to consider surgery especially if the Afirma is reported to be suspicious.

However, it is important to appreciate the risk of malignancy is still ~40% and not 100%. Afirma is also more likely to be positive in patients presenting with Hashimoto thyroiditis, and it is always confusing in Hurthle cell lesions as it invariably turns out to be suspicious. Obviously, some of these decisions are best made by the clinician based on other clinical and radiologic features and parameters. ThyroSeq Thyroid Cancer Next-Generation Sequencing Panel is also used in indeterminate nodules by FNA (Bethesda categories III, IV, V) and malignant nodules when molecular testing is expected to affect the decision to perform surgery or extent of surgery. Mutations in thyroid cancer–related genes and gene fusions are detected by next-generation sequencing. This may also be useful in clinical decision making with regard to administration of radioactive iodine, intensity of follow-up, and targeted therapies.[15] An algorithm for the evaluation of the thyroid nodule is provided in Figure 19.5.

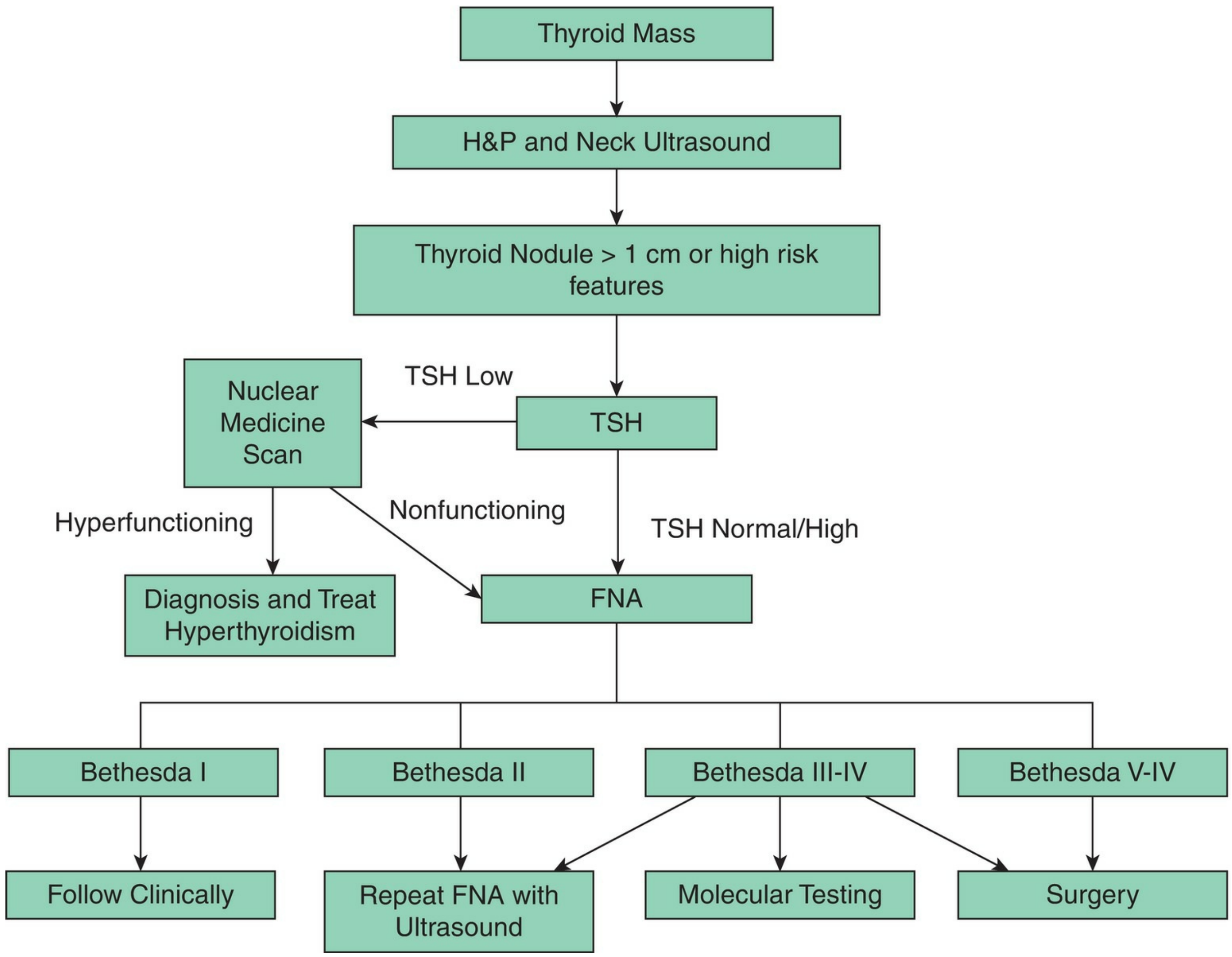

Figure 19.5. Evaluation of thyroid nodule.

MOLECULAR BIOLOGY OF WELL-DIFFERENTIATED THYROID CANCER

Noteworthy advances in the understanding of the molecular biology of thyroid cancer are beginning to be incorporated into clinical practice. The Cancer Genome Atlas Research Network recently reported on genomic landscape of 496 papillary thyroid cancers (PTCs).[16] The genome of PTC is described as relatively "quiet," as compared to other cancers as defined as a low frequency of somatic alterations, and this may offer a biologic basis for the indolent clinical behavior of PTCs. Common known drivers will be discussed in greater detail.

Proto-oncogenes Associated with Thyroid Cancer

Chromosomal Rearrangements (RET/PTC)

Rearrangement of the RET proto-oncogene *RET* results in the aberrant production of chimeric forms of the receptor (RET/PTC) in thyroid cells, which leads to constitutive activation of several downstream pathways, including mitogen-activated protein kinase (MAPK), extracellular signal-related kinase (ERK), and phosphatidylinositol 3-kinase (PI3K). This rearrangement has been observed in post-Chernobyl pediatric thyroid cancers (RET/PTC1) and has been associated with classical PTC, as well as solid variant PTCs (RET/PTC3).[17]

Ras Oncogenes

The 3 classical Ras proto-oncogenes encoding Hras, Kras, and Nras belong to an extended family of small G proteins. *Ras* mutations are found in follicular adenomas and carcinomas[18] and are also observed in 13% of PTCs.[16,19] Ras mutations are thought to be an early event in thyroid cancer genesis and some have shown they follow a more aggressive clinical course.[20]

BRAF and MAP Kinase Signaling Pathway

The BRAF missense mutation in exon 15, which leads to the substitution of the amino acid valine for glutamic acid at residue position 600, is the most frequent genetic change in PTC and has been observed in 60% of tumors.[16] Mutant BRAF is a potent activator of the downstream effectors, the MAP kinases in the Raf–MEK–ERK pathway, which mediate cellular responses to growth signals. Clinically, PTCs with BRAF mutations are more common and are associated with an aggressive clinical course including extrathyroidal invasion, greater rates of recurrence, and treatment failure,[21] which translates into worse clinical outcomes.[22]

BRAF mutation has also been shown to be responsible for the suppression of expression of the sodium/iodide symporter (NIS) leading to RAI resistance.[23] Inhibitors of the BRAF kinase have been developed and show promise in treating several cancer types. However, development of resistance to BRAF kinase inhibitors is common. In addition, inhibitors of the MAP kinase pathway have been developed and are beginning to be used clinically.

Well-Differentiated Thyroid Cancers

Papillary and follicular carcinomas collectively grouped as differentiated thyroid cancer constitute more than 90% of all malignant neoplasms of the thyroid gland. These two entities share similar diagnostic and treatment algorithms and have an overall excellent prognosis of 97.8% at 5 years when diagnosed and treated appropriately.

Staging and Prognostic Schemas

Cancer staging is an essential prognostic tool that is integral part of cancer management. The familiar tumor–nodal–metastasis (TNM) staging system is the most widely applied staging system in thyroid cancer. Unique to thyroid cancer, age at diagnosis is incorporated in the staging system reflecting its marked influence on outcome. The American Joint Committee on Cancer (AJCC) 7th edition (Tables 19.1 and 19.2) has been shown to predict differentiated thyroid cancer–related death.[24] The prognostic factors in thyroid cancer are well defined and reported from several independent datasets, starting from the EORTC study published in 1979.[25] In the United States, Cady of the Lahey Clinic and Hay et al. of the Mayo Clinic reported similar prognostic factors in the 1980s.[26,27] The Mayo Clinic revisited their data and included completeness of resection as an important prognostic factor leading to their acronym of MACIS.[28] Memorial Sloan Kettering Cancer Center subsequently also suggested similar prognostic factors with the acronym GAMES (grade of the tumor, age, distant metastasis, extrathyroid extension, and size of the tumor).[29] These schemas are summarized in Table 19.7. A risk-stratified approach has also been adopted in the ATA guidelines and is summarized in Table 19.8.

Table 19.7 Prognosis Schemas of Well-Differentiated Thyroid Cancer

Lahey Clinic[17]	Mayo Clinic[19]	MSKCC[30]
A—Age M—Metastasis E—Extent S—Size	M—Metastasis A—Age C—Completeness of surgical resection I—Invasion S—Size	G—Grade of the Tumor A—Age M—Metastasis E—Extrathyroidal extension S—Size

Table 19.8 Three Level Risk Stratification of Recurrence

Low Risk	Intermediate Risk	High Risk
No local or distant metastases complete resection, no gross disease No locoregional invasion tumor does not have aggressive histology No vascular invasion no 131I uptake outside the thyroid bed on the first posttreatment whole-body RAI scan	Microscopic invasion into the perithyroidal soft tissues Cervical lymph node metastases 131I uptake outside the thyroid bed Aggressive histology or vascular invasion	Gross tumor invasion, incomplete tumor resection Distant metastases Thyroglobulinemia out of proportion to posttreatment scan

Adapted from ATA Guidelines 2009 version.

Histologic Classification of Thyroid Cancers Arising from Follicular Cells

Thyroid cancer represents a spectrum of tumors with different biologic behavior. At one end of the scale, there are the differentiated carcinomas with excellent prognoses, whereas, at the other end of the spectrum, there is anaplastic thyroid cancer (ATC), which has an almost universally fatal outcome. As tumor histology becomes less differentiated, radioactive iodine avidity decreases whereas FDG PET uptake increases. This is also associated with a worse prognosis.[31] We will discuss the tumors on this spectrum from PTC and their multiple clinically relevant variants to follicular thyroid carcinoma (FTC) followed by poorly differentiated thyroid cancer (PDTC) and finally ATC.

Papillary Carcinoma and Variants

PTC is a primary thyroid cancer of follicular epithelial cell origin defined by distinctive nuclear features. Classic nuclear features that define PTC include nuclear crowding with overlap, nuclear enlargement, chromatin clearing or

ground-glass appearance (“Orphan Annie nuclei”), nuclear elongation, nuclear grooves, irregular nuclear membranes, intranuclear cytoplasmic inclusions, and eccentric inconspicuous nucleoli.[32]

Variants of PTC based on histologic feature are reported and are of clinical and prognostic relevance.

Tall Cell Variant

Tall cell variant is rare but associated with an aggressive clinical course. It is histologically defined as cells having a height that is at least twice the width of the cell, eosinophilic cytoplasm, along with characteristic nuclear features of papillary carcinoma (Fig. 19.6). There is a high prevalence of the BRAF mutations observed as high as 80% to 100% in tall cell variant of PTC.[33] Clinically, there is a higher frequency of extrathyroidal extension, higher stage, larger size, and older age (mean 57 years) at presentation. These tumors are commonly PET avid and often do not concentrate RAI.[34]

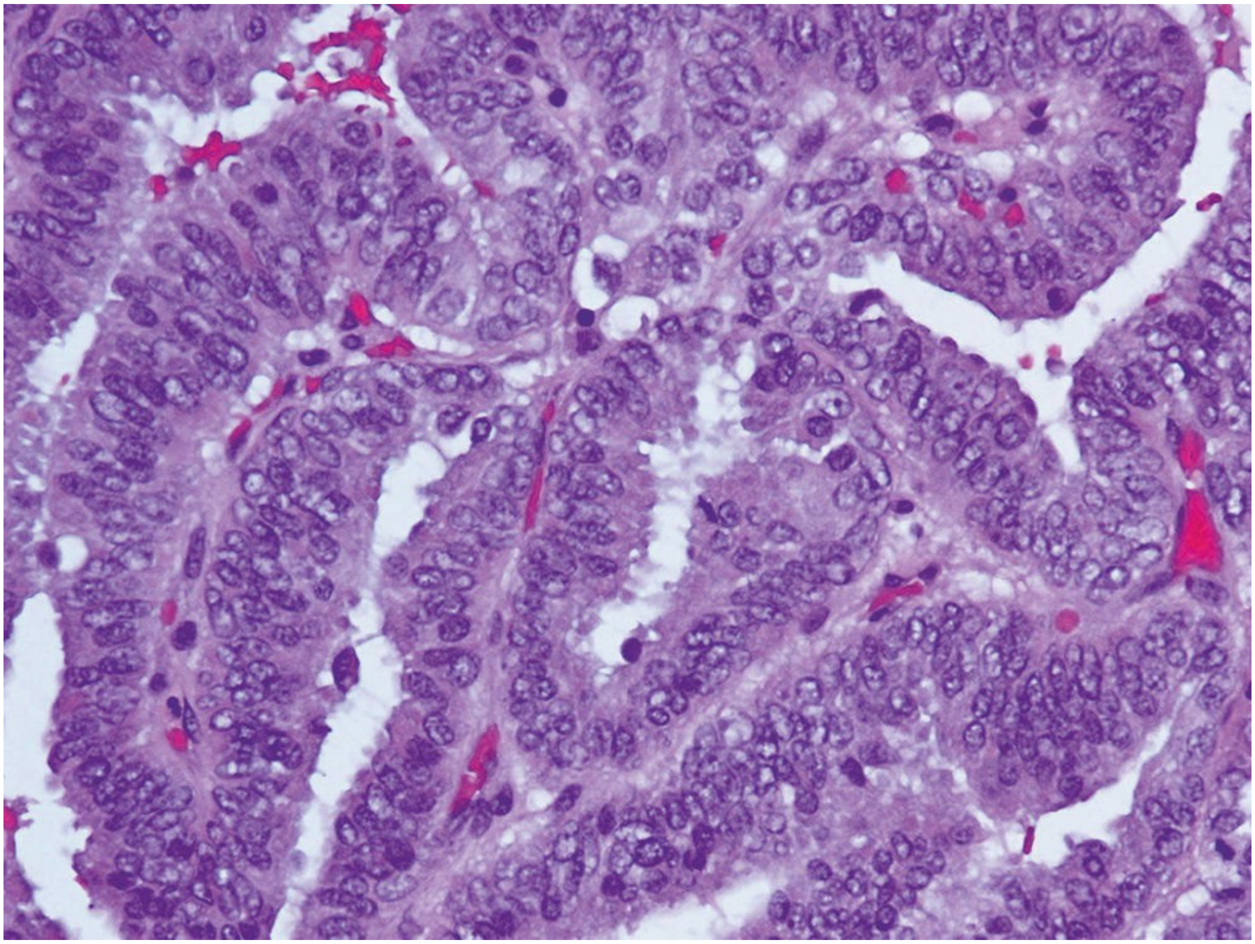

Figure 19.6. Tall cell variant of papillary thyroid cancer. Histologically defined as cells with a height that is at least twice the width with characteristic nuclear features of papillary carcinoma.

Columnar Cell Variant

The columnar variant of PTC has an aggressive clinical course, histologically associated with elongated columnar cells, with prominent nuclear stratification and elongated nuclei. In contrast to classic PTC, intranuclear cytoplasmic inclusions may not be found and nuclear grooves may be rare. These tumors are more often associated with extrathyroidal extension, recurrence, and aggressive local growth when the tumor is well encapsulated and metastases are rare.[35]

Diffuse Sclerosing Variant

Diffuse sclerosing variant is another biologically aggressive histology of

PTC, which is known to present at a younger age (mean age 18 years; range 6 to 49 years) in the setting of thyroiditis. These tumors are more often bilateral and show increased stromal fibrosis and sclerosis, squamous metaplasia, lymphocytic infiltrate, and psammoma bodies.[36]

Cribriform–Morular Variant

Clinically, this lesion is important for its association with the familial adenomatous polyposis (AFP) syndrome. When associated with AFP, tumors of this subtype are more commonly found to be multifocal and bilateral; therefore, total thyroidectomy is recommended. These tumors tend to follow an indolent course.[37]

Solid Variant

If >50% of the tumor shows a focal solid growth pattern, the solid variant of PTC is diagnosed. Clinically, these tumors are associated with prior exposure to radiation and are seen in children. Thirty percent of cases that have been reported are associated with the Chernobyl nuclear accident.[38] Nikiforov et al.[39] showed that cases of solid variant PTC are associated with a slightly higher frequency of distant metastases and less favorable prognosis than classical PTC.

Follicular Variant of Papillary Thyroid Carcinoma

The follicular variant of papillary thyroid carcinoma (FVPTC) is a common subset of (PTC) and is found in up to 24% of patients with PTC.[40] This variant is composed entirely or almost completely of follicles, which are lined by cells that have the nuclear features of papillary carcinoma. FVPTC appears to be a heterogeneous disease composed of 2 distinct groups: an infiltrative/diffuse (nonencapsulated) subvariant, which resembles classic PTC in its metastatic lymph node pattern and invasive growth, and an encapsulated form, which behaves more like follicular adenoma/follicular carcinoma.[41] Consistent with this statement, Baloch et al.[42] showed that encapsulated FVPTCs can metastasize to distant sites in the absence of cervical lymph node metastases, mimicking the behavior of FTC. Nonencapsulated FVPTCs that are invasive are easily diagnosed as cancer.

However, the encapsulated form diagnosed solely on nuclear features

consistent with PTC can be more difficult. In a retrospective analysis of the MSKCC thyroid database, Liu et al. reported that the rate of lymph node metastasis was significantly higher in patients who had nonencapsulated tumors. In addition, patients with encapsulated tumors had no recurrences; the authors concluded that encapsulated FVPTCs could be treated by lobectomy alone.

Follicular Carcinoma

Follicular carcinoma of the thyroid gland accounts for between 4% and 39% of all malignant thyroid tumors and lacks the nuclear features associated with PTC.[43] FTC is differentiated from follicular adenoma by the presence of capsular invasion and vascular invasion. In contrast to PTC, which has a propensity to metastases via lymphatics, FTC more commonly disseminates systemically in the form of distant metastasis. These characteristics should be taken into consideration when planning primary management and surveillance. A large number of previously reported follicular carcinomas were probably FVPTC.

Hurthle Cell Carcinoma (HCC)

Although once thought to be an oncocytic variant of follicular carcinoma, genetic profiling has provided evidence that this entity may be a unique thyroid cancer distinct from papillary and follicular thyroid cancer.[44] HCC accounts for 3% to 4% of all thyroid cancers[45] and is characterized by large cells with hyperchromatic nuclei and an abundant granular cytoplasm containing large numbers of mitochondria.[46] Like FTC, malignancy cannot be diagnosed without the identification of capsular or vascular invasion. Patients with the widely invasive form of HCC have a poor prognosis compared to those with PTC and FTC with a recurrence rate of 31% and disease-specific mortality of 25% and a high incidence of metastasis.[47,48]

POORLY DIFFERENTIATED THYROID CANCER

PDTC represents a middle ground between well-differentiated, papillary carcinomas and the usually lethal, anaplastic carcinomas. These tumors

occupy an intermediate position both clinically and histologically. There has been some debate regarding the histologic definition. The Turin proposal of PDTC included (1) presence of a solid/trabecular/insular pattern of growth, (2) absence of the conventional nuclear features of papillary carcinoma, and (3) presence of at least one of the following features: convoluted nuclei, mitotic activity ≥3 × 10 HPF, and tumor necrosis.[49] At Memorial Sloan Kettering Cancer Center, PDTC is defined by the presence of necrosis and/or a high mitotic rate, irrespective of growth pattern and cell type.[50] These features were shown to define clinical behavior independently of architectural grade, and PDTC defined on the basis of mitoses and/or necrosis are associated with RAI refractoriness, uptake of fluorodeoxyglucose on positron emission tomography, and positive and high rates of recurrence. Additionally, using this definition, overall survival was found to be 60%, which is intermediate between differentiated and AT cancer.

MANAGEMENT OF THYROID CANCER

Management of thyroid cancer requires a multidisciplinary approach involving a surgeon, endocrinologist, pathologist, nuclear medicine physician, and, sometimes, a medical oncologist. Evaluation first starts with a through history and physical examination. Symptoms indicative of vocal cord paralysis such as hoarseness, dysphagia, odynophagia, and aspiration should raise concern for aggressive tumors invading the RLN. A full examination of the head and neck should be performed. Emphasis should be placed on evaluation of the thyroid gland, lateral neck, and larynx. It is important to recognize that vocal fold impairment can be present independent of voice changes.

Ultrasound (US) is often the first modality utilized to evaluate a thyroid cancer because it is readily accessible, inexpensive, and noninvasive and it requires no radiation exposure. US is effective at delineating intrathyroidal architecture as well as in the evaluation for lymph node metastasis.

Physical examination sometimes points to involvement of surrounding structures in invasive thyroid carcinoma. Occasionally, to optimally evaluate the locoregional extent of the disease, cross-sectional imaging with a CT scan is indicated. CT scanning is best performed with contrast even though there is a general concern about use of contrast and iodinated dye, which may inhibit

the early use of radioactive iodine ablation. A CT with contrast is quite helpful to the operating surgeon for surgical planning, especially in patients initially presenting with locally advanced disease, such as those with fixed disease in the central compartment adherent to the trachea and esophagus or a paralyzed vocal cord. A CT scan with contrast is also important to evaluate the extent of the lymph nodal metastasis, extent of the paratracheal disease, and extension to the superior mediastinum. It is also helpful to evaluate if there is any presence of retropharyngeal or parapharyngeal disease, which is important to appreciate prior to surgery as this disease is generally not well imaged on a routine ultrasound.

THYROIDECTOMY

The surgery begins with patient positioning and planning of the incision. An incision is first marked and concealed in a natural skin crease. This is done in the preoperative holding area with the patient seated. In young women, a more cranial incision is preferred. In general, the incision should be made just inferior to the cricoid cartilage. Alternatively, a higher skin crease can be selected (Fig. 19.7). Incision length should be based on the extent of the surgery planed, size of the patient, neck configuration, and extent of disease. For example, if a neck dissection will be required as part of the first procedure or likely in future procedures, the incision should be placed adjacent to the cricoid cartilage as this position gives exposure to the entire neck and the J-shaped or apron incision can be avoided. Although cosmetic concerns should be considered, the operating surgeon needs to plan an incision that will allow for the exposure needed for complete resection of the thyroid cancer as this represents the major factor for best control of disease. The planned incision site is infiltrated with lidocaine and epinephrine to avoid excessive bleeding from the skin and subcutaneous tissues.

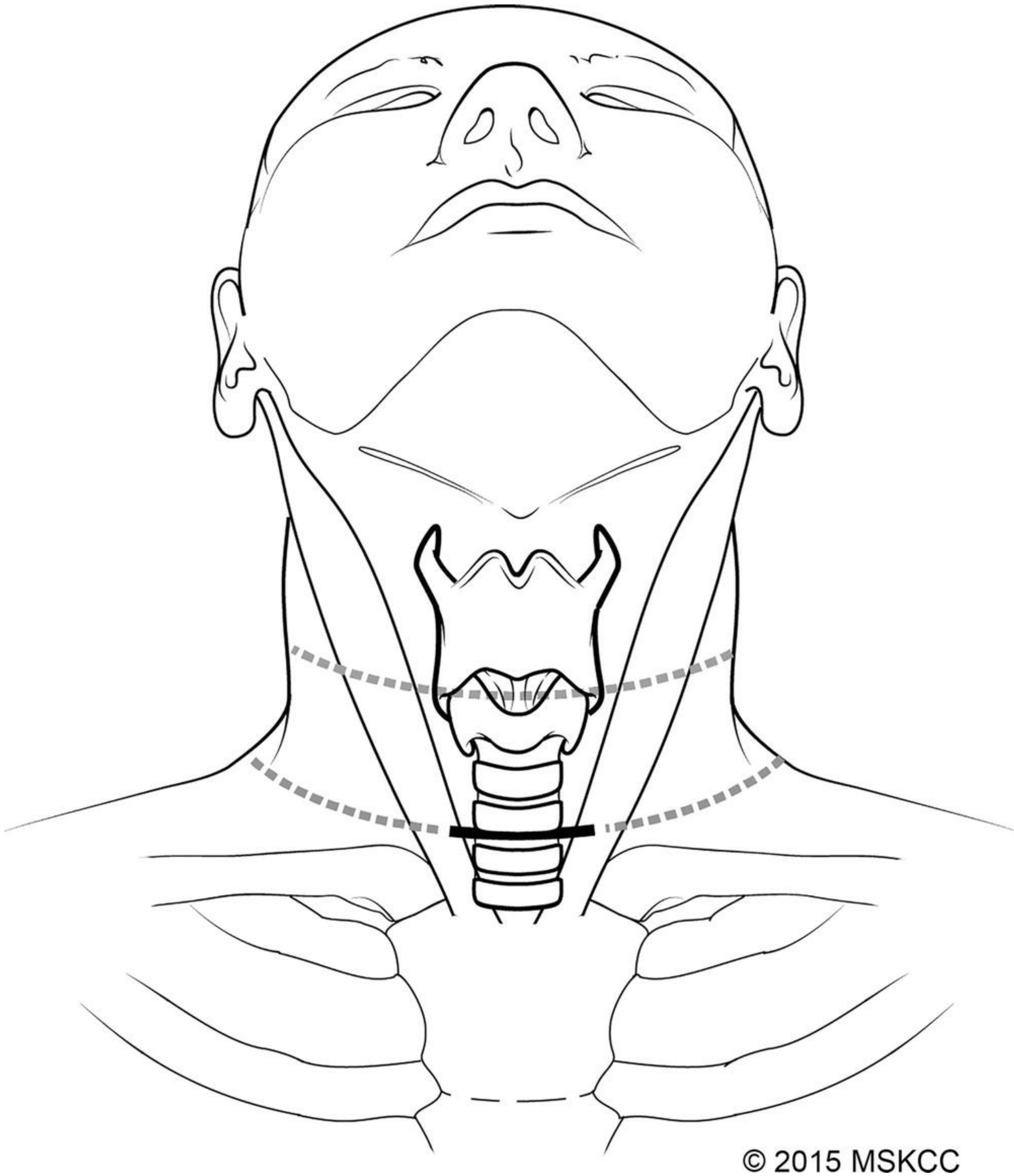

Figure 19.7. The incision should be made just inferior to the cricoid cartilage. Alternatively, a higher skin crease can be selected, which gives better access to the superior pole vessels.

The optimal positioning is with a standard supine position with arms padded and tucked. The head is extended and the operating table is

maintained in a reverse Trendelenburg position. A transparent plastic drape allows continuous monitoring of the endotracheal tube and anesthesia circuit (Fig. 19.8). The skin is incised with a knife and then most of the remaining dissection is undertaken with unipolar or bipolar electrocautery. For the subcutaneous tissue, pointed electrocautery is used and subsequently a flat electrocautery is used. Once the incision is deepened through the subcutaneous tissue, the platysma muscle is incised. The platysma is sparse in the midline and therefore is better identified laterally. A subplatysmal flap is then raised. The superior flap is elevated under traction with the use of skin hooks where the plane is avascular to the thyroid notch. An inferior flap is then undermined as far as the sternal notch (Fig. 19.9). The midline fascia is then exposed and should be incised running parallel to the muscle. Often, there is a bridging vein communicating between the two anterior jugular veins, which should be dissected and ligated. The strap muscles are then separated in the midline. Opening this area is much like opening a “gift” box,[51] with the thyroid contained inside of the strap muscles and investing fascia. The anterior most strap muscle (sternohyoid) is then easily separated and retracted laterally. The sternothyroid is then exposed. There is debate about cutting the inner strap muscle. We generally prefer to cut the sternothyroid muscle superiorly and inferiorly from both an oncologic point and for better exposure of the superior thyroid pole. Attention is then turned from midline dissection to lateral dissection. The middle thyroid vein is identified, clamped, and ligated. Gentle dissection is performed inferiorly to expose the tracheoesophageal groove.

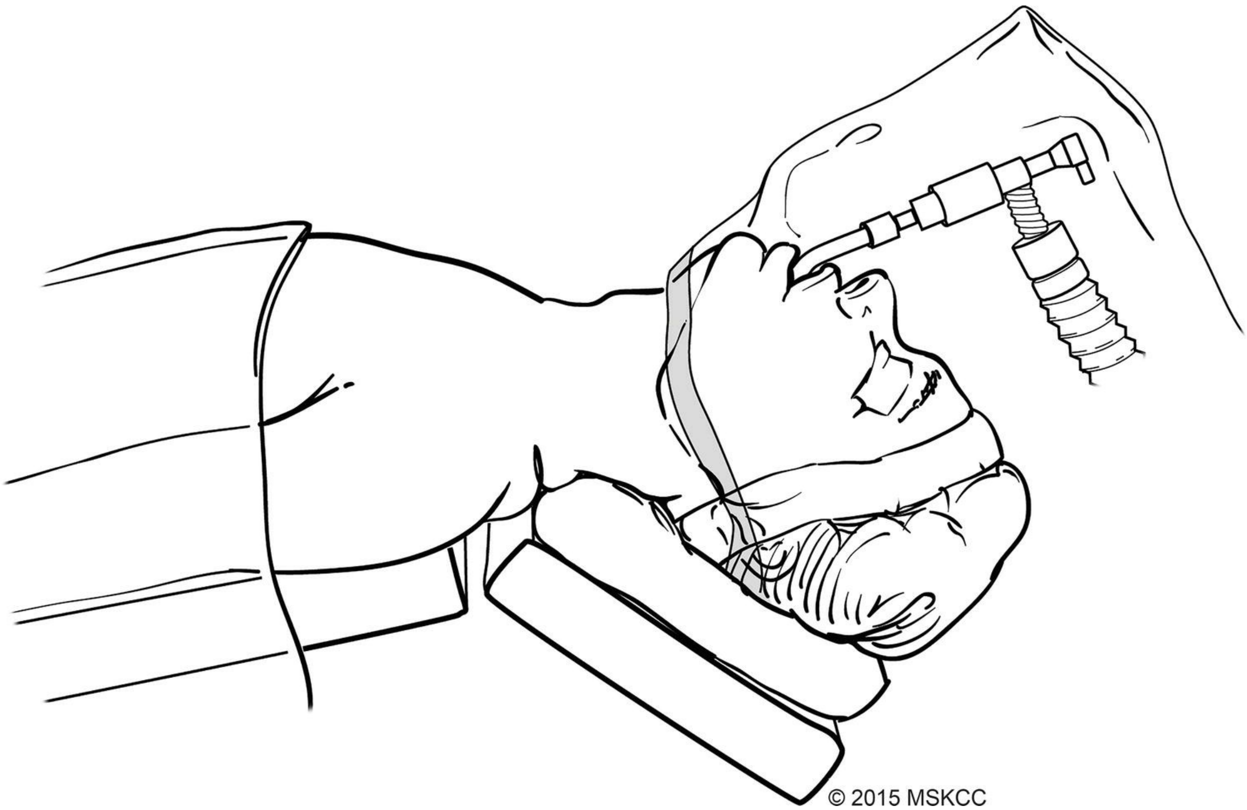

Figure 19.8. The patient is positioned supine on the operating table, which is maintained in a reverse Trendelenburg position with the neck extended.

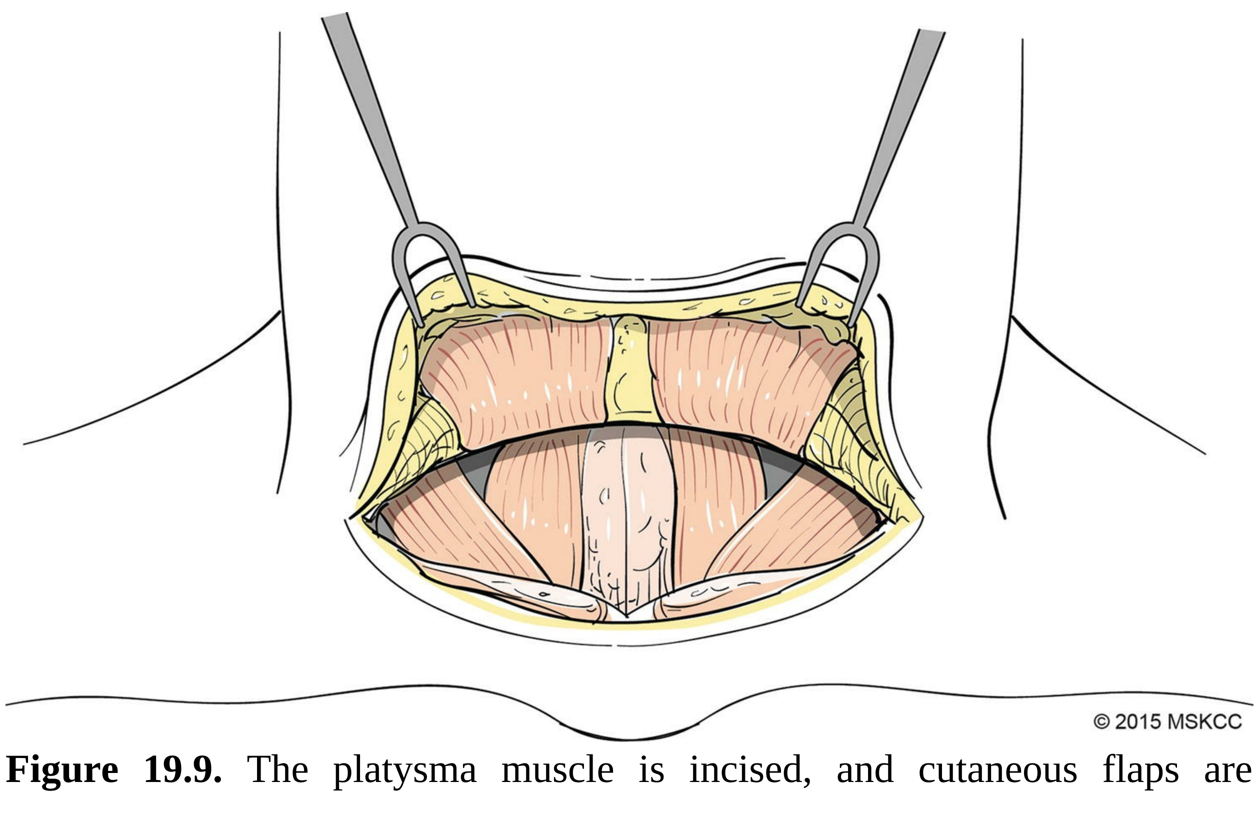

Figure 19.9. The platysma muscle is incised, and cutaneous flaps are

developed in the subplatysmal plane.

Attention is then turned to the superior pole. It is first exposed and a clamp is placed on the upper portion of the thyroid lobe. Retraction with the clamp helps to pull the thyroid in an inferior and lateral direction. This maneuver opens the medial aspect of the superior thyroid vessels known as Joll’s triangle. In this area, attention must be paid to the tiny veins arising from the superior thyroid vein. These should be cauterized. With gentle traction of the superior pole vessels in the inferolateral direction, the external branch of the superior laryngeal nerve should be identified. Approximately 40% to 50% of the time, the superior laryngeal nerve may be difficult to identify, and therefore, individually clamping and ligating the superior pole vessels close to the thyroid gland are important to avoid injury to the superior laryngeal nerve.

Vessels can be tied or controlled with harmonic scalpel or LigaSure. Dissection is then once again directed laterally. When dissecting on the right side, consideration should be given to evaluate if the patient has a nonrecurrent LN. The dissection continues on the lateral aspect of the thyroid gland while retracting the gland medially. Finger retraction of the thyroid lobe is used during dissection of the paratracheal area as use of Allis or Lahey clamp can result in capsular trauma and bleeding from the thyroid gland. As the superior pole and lateral thyroid gland is exposed, the tracheoesophageal groove area should also be exposed. There is always a tiny vein in front of the cricoid cartilage, which should be ligated as this may be a source of bleeding postoperatively.

Parathyroid glands can be identified in the superior and inferior portion of the thyroid gland in front of and behind the RLN. Occasionally, the parathyroid glands may be within the thyroid capsule. In these cases, careful dissection with separation of the thyroid from the parathyroid gland is required to avoid bleeding. Every effort should be taken to avoid disrupting the blood supply to the parathyroid glands. When the inferior thyroid artery is ligated, care should be taken that is close to the thyroid gland in order to preserve blood supply to the parathyroid gland (Fig. 19.10). If at the end of the operation the gland appears devascularized, it should be autotransplanted into the sternocleidomastoid muscle on the side contralateral from the tumor. Frozen section conformation of parathyroid tissue should be performed

before reimplantation, in order to avoid implantation of lymph nodes or metastatic carcinoma. The area of implantation is marked with a silk stitch for future reference.

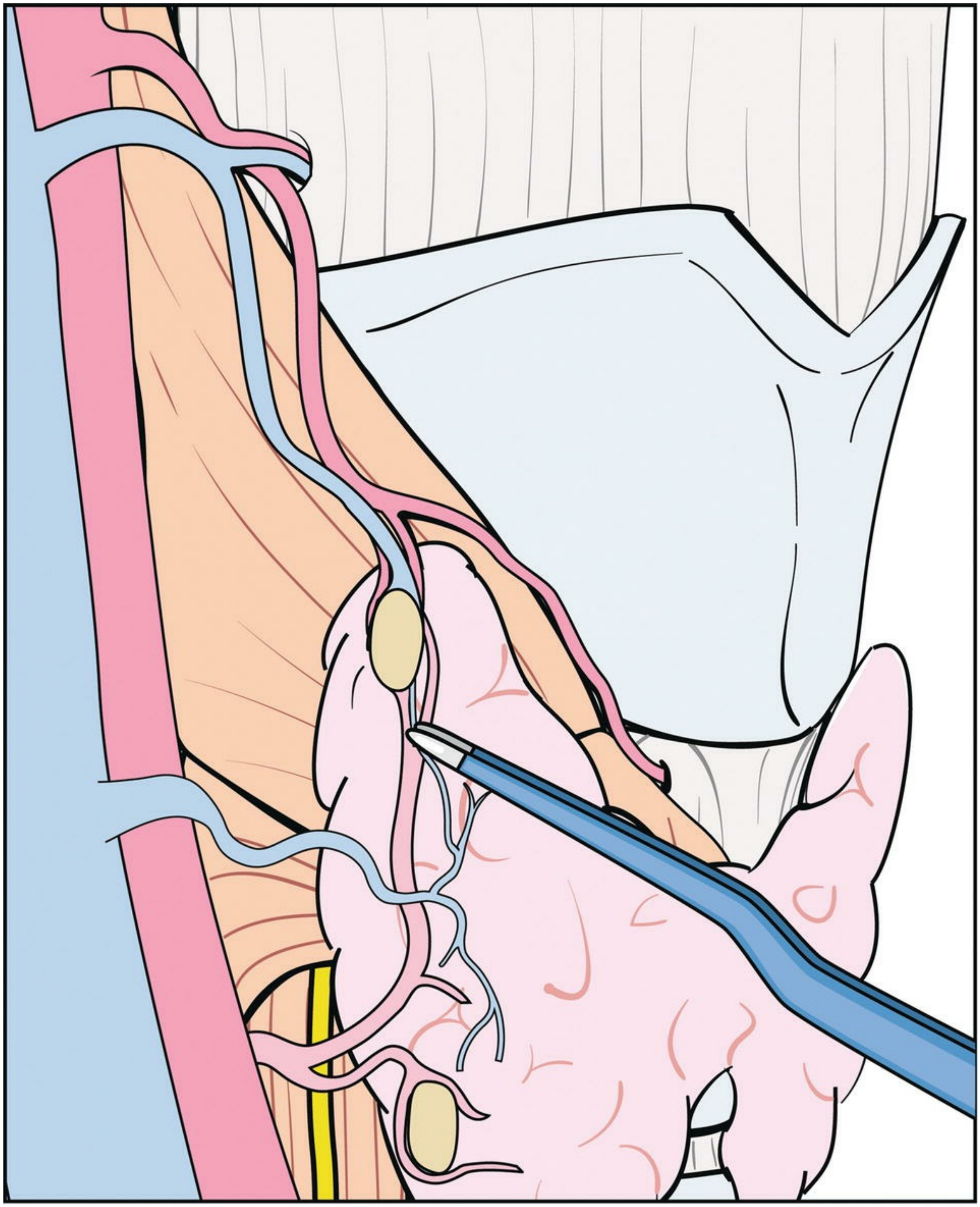

Figure 19.10. In order to preserve blood supply to the parathyroid gland, the inferior thyroid artery is ligated close to the thyroid gland.

Continuing laterally, the tuberculum Zuckerkandl is then identified. The RLN is generally located posterior to this structure. This can be identified by retraction of the tuberculum. Identification of the RLN is then carried out. It can be identified in three distinct areas. First, it can be identified in the tracheoesophageal groove and traced superior until the cricoid cartilage. This is a useful strategy in patients with suspicious lymph nodes. Second is at the intersection of the nerve and inferior thyroid artery. In most patients, the nerve courses under the inferior thyroid artery; however, in 25% of patients, it crosses over and this anatomic variability needs to be considered when using this technique (Fig. 19.11). Our practice is to identify a short segment near Berry's ligament behind tuberculum Zuckerkandl. The operation slows during dissection in the region of the ligament of Berry and the tuberculum Zuckerkandl as this is a critical portion of the operation and meticulous dissection is essential. During this portion of the operation, the thyroid gland is retracted medially; however, it must be realized that traction injury secondary to forceful retraction can result in nerve palsy. The tumor may involve the RLN. In these cases, if the nerve is functioning preoperatively, the tumor can usually be peeled off of the nerve. If instead the nerve is directly involved with tumor and there is a possibility of leaving gross tumor behind, resection of the ipsilateral nerve may be required. Prior to resection of a functioning nerve, the contralateral lobe should be mobilized with preservation of the contralateral RLN. The gland is then released from the laryngeal cartilage by identifying and transecting the ligament of Berry. During the release of the ligament of Berry, control of bleeding from tiny vessels, which run in the ligament, will be required. One must be careful in this area as the nerve is quite close and bipolar cautery with fine-tip forceps should be used to reduce heat to surrounding tissues while maintaining precise control of bleeding. If suture material is required in this area, something that is dissolvable such as polyglactin or chromic gut is advantageous. The inferior thyroid veins, which are often numerous and run parallel to the RLN or trachea, should be ligated carefully. Sometimes, an arteria thyroidea ima vessel from the brachiocephalic trunk along the trachea will be present. This vessel can retract into the mediastinum and can cause bleeding that is difficult to control, and therefore, it is important to be vigilant for this vessel and to identify and ligate it with care.

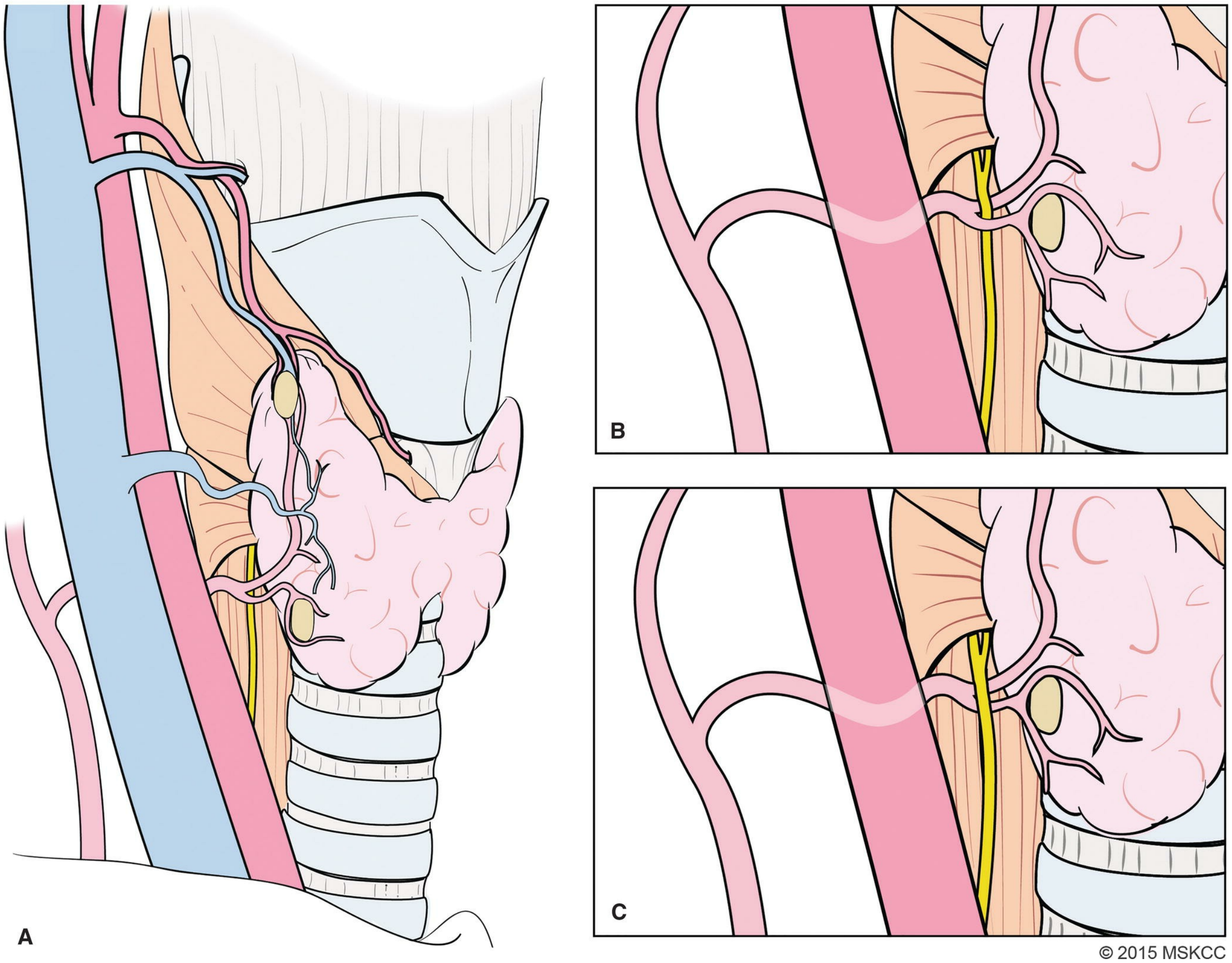

Figure 19.11. Anatomy of inferior thyroid artery **(A)**. In most patients, the nerve courses under the inferior thyroid artery **(B)**; however, in 25% of patients, it crosses over the inferior thyroid artery **(C)**.

After the entire gland is mobilized, the dissection continues on the surface of the trachea in the avascular pretracheal plane. The extent of thyroidectomy will depend on the philosophy of the operating surgeon and the disease process at hand. Generally, a true extracapsular thyroidectomy is done for patients with malignancy. Sometimes, a small portion of thyroid tissue may be left near the ligament of Berry, the superior pole, or in the pyramidal lobe area.

In some cases of locally advanced thyroid carcinoma, the tumor may be adherent to the trachea. At this time, the surgeon must make a critical decision about removing the tumor from the trachea. Obviously, if the tumor is invading the trachea, tracheal resection will be required. However, if there

is no invasion, the tumor can often be shaved off the trachea with careful attention to avoid inadvertently violating the trachea.

Once the thyroid gland has been mobilized out of the surgical bed, the field is inspected. Some surgeons may consider transecting the isthmic area before proceeding to the other side; however, we usually leave the specimen intact and proceed to other side for completion of the thyroidectomy by repeating the discussed steps. Hemostasis should be confirmed and the tracheoesophageal groove should be examined for suspicious lymph nodes. If there are suspicious lymph nodes present, they should be excised and analyzed by frozen section. If positive for malignancy, the central compartment should be dissected. Some surgeons perform an elective central neck compartment dissection in high-risk patients. Appropriate evaluation of the superior mediastinum for metastatic lymphadenopathy is also important.

At the conclusion of the procedure, we prefer to only use minimal irrigation of the wound because excessive irrigation may disrupt parathyroid glands or result in accidental suctioning a gland out of the surgical bed. At the end of the procedure, a Valsalva maneuver is requested from the anesthesiologist to confirm that there are not any bleeding areas. The strap muscles are then approximated in the midline with two sutures. Watertight closures are avoided, which may worsen airway effects in the case of a postoperative hematoma. The platysma is then approximated with polyglactin sutures and the skin is closed with a running subcuticular absorbable suture. Figure 19.12 demonstrates total thyroidectomy specimen with a dominant nodule. Drains are rarely used in standard total thyroidectomy but are commonly used in patients with large substernal goiters or those with bleeding during surgery. Drains are also used in patients who require more extensive dissection such as in those with Grave disease or Hashimoto thyroiditis. If a drain is used, a closed suction drain is recommended and can be removed in most patients 24 hours after surgery prior to discharge.

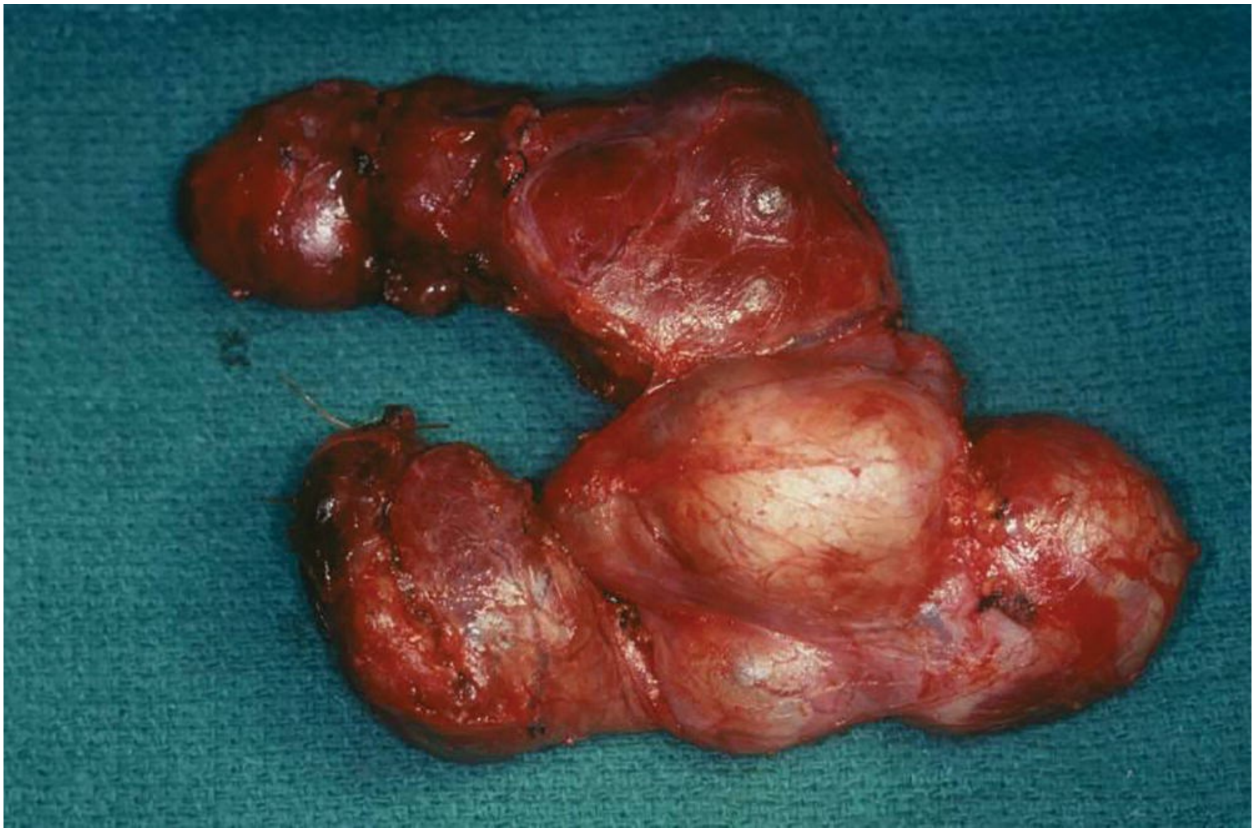

Figure 19.12. Total thyroidectomy specimen with dominant nodule.

POSTOPERATIVE CARE AND COMPLICATIONS

A hematoma may develop in the acute postoperative period. Although small collections can simply be observed, an expanding hematoma requires urgent attention. Because of the close proximity of the surgical field to the airway, in severe cases, the surgical incision should be opened at the bedside, thereby removing pressure on the central compartment and airway. Once the acute airway pressure has been alleviated, the patient should be returned to the operating room for exploration of the wound, control of hemorrhage, and irrigation.

Transient parathyroid dysfunction may be observed commonly after thyroid surgery, and therefore, it is recommended that patients be monitored clinically as well as biochemically after total thyroidectomy. Serum calcium that has been corrected to account for albumin or ion calcium is often used. Postoperative intact PTH has been shown to predict need for

hypoparathyroidism and need for calcium supplementation.[52] Some patients will require calcium with or without vitamin D postoperatively. Most patients can be weaned from this supplementation as most cases are transient and resolve in 4 to 6 weeks.

Permanent RLN injury is uncommon, occurring in 1% to 2% of cases. Transient injuries in the presence of a preserved nerve are most often related to traction and will usually recover spontaneously. In cases where there has been significant prolonged vocal fold dysfunction, or permanent paralysis, a medialization procedure can be considered.

More common and less recognized is injury to the external branch of the superior laryngeal nerve. Patients will often present with the complaint of not being able to "hit high notes" or yell after surgery. Identifying this nerve as well as taking superior pole vessels close to thyroid and individually is helpful in preserving function of this nerve postoperatively.

SUMMARY OF ATA RECOMMENDATIONS FOR MANAGEMENT OF PRIMARY TUMOR AND CERVICAL LYMPH NODES

The ATA has played an important role in developing guidelines for well-differentiated thyroid cancer over the last 10 years. The first edition of these guidelines was published in 2006 and the revised edition was published in 2009. A new edition with considerable revisions will be published in 2015 and it is based upon a deep understanding of the biology of thyroid cancer, risk group stratification, prognostic factors, and judicious use of adjuvant therapies including radioactive iodine ablation. The ATA guidelines include both patient and tumor factors and stratify the patients into low-, intermediate-, and high-risk groups for recurrence of thyroid cancer. This risk classification is very important in the primary management of thyroid cancer. The extent of thyroidectomy, which was defined initially as total thyroidectomy for tumors more than 1 cm, has been revised considerably and a lobectomy may be performed for intrathyroidal tumors up to 4 cm. The NCCN guidelines have always adhered to the role of lobectomy in patients

with intracapsular thyroid tumors up to 4 cm. However, the ATA has changed the guidelines now to adhere to the overall principles of more conservative management of low-risk thyroid cancer. The understanding of the risk group's stratification is critical in the determination of the extent of thyroidectomy and the need for paratracheal and/or lateral nodal dissection and adjuvant treatment. It appears from the most recent guideline that the extent of thyroidectomy can be limited to lobectomy with isthmusectomy in selected patients with low-risk thyroid cancer or intrathyroidal tumors where the quality of life is thought to be enhanced in patients who still have a natural source of thyroid hormones. Naturally, some of these patients may need additional supplementation with thyroid medication even though they have native thyroid tissue in situ. It is important to note that the opposite lobe needs to be followed to see if patients will develop further nodularity or even obvious cancer in the opposite lobe at which time they will definitely require completion thyroidectomy.

A major debate remaining in the management of thyroid cancer concerns the role of prophylactic central compartment dissection and the extent of lateral neck dissection. In the first edition of the ATA thyroid guidelines, there was a statement made about the use of prophylactic nodal dissection in patients presenting with tumors more than 1 cm. However, it was soon apparent to the surgical community that if more prophylactic neck dissections are performed, there is a greater likelihood of nerve injury and temporary and permanent hypoparathyroidism. Therefore, there is not a strong rationale to perform routine prophylactic node dissection especially in the low-risk thyroid cancer patients. Although ~40% to 50% of the patients will have microscopic nodal disease in thyroid cancer, the removal of these microscopic foci of metastatic tumor has very little impact on the long-term survival and outcome, providing a strong rationale for closely observing as opposed to electively dissecting the central compartment. Nevertheless, in individuals who are older and have bulky nodal disease or aggressive histology, the removal of the central compartment nodes should be considered. This is reflected in the second edition of ATA guidelines, which recommends prophylactic nodal dissection in high-risk patients, such as T3 and T4 tumors, or patients presenting with extrathyroidal extension of the disease or aggressive histology.

The extent of the lateral neck dissection in patients with clinically or

radiologically apparent nodal metastasis remains the selective neck dissection of level II to level V. The incidence of metastatic disease at level I is so low that unless there is gross metastatic disease at level II, level I can be spared. Similarly, level Va nodal metastasis is quite rare and this region can be spared in an effort to avoid injury to the spinal accessory nerve. Similarly, nodal metastasis to level IIb is quite rare in thyroid cancer and this region can be easily spared in an effort to avoid traction injury to the accessory nerve.

There is also considerable interest in avoiding the routine use of radioactive iodine ablation especially in low-risk thyroid cancer patients. There does not appear to be any major benefit of routine use of radioactive iodine in low-risk patients, as there is a high incidence of complications such as chronic sialadenitis and dry mouth as well as a slightly higher incidence of second primary tumors. Postoperative surveillance by monitoring serum thyroglobulin level is also quite helpful to make certain decisions regarding adjuvant treatment with RAI. However, there is a general consensus currently to avoid RAI in most of the low-risk thyroid cancer patients.

MINIMALLY INVASIVE THYROIDECTOMY (MIT)

In the recent past, there has been great interest in thyroidectomy through a “minimally invasive” approach. Much of the interest has come from surgeons who have observed the benefits of minimally invasive techniques in general surgery, cardiothoracic surgery, and orthopedic surgery. Where there have been numerous published reports of decreased pain, shorter hospital stay, and improved patient satisfaction, a smaller or completely absent scar on the neck has been a commonly reported outcome of MIT.

MIT can be divided into two broad categories. These include those in which the thyroid is approached through a small incision in the neck and thyroidectomy in which the approach is extracervical. We will discuss the four approaches: nonendoscopic MIT, endoscopic thyroidectomy through a neck incision, robotic assisted via axilla and breast, and robotic assisted via a facelift approach.

Nonendoscopic Minimally Invasive Thyroidectomy

The minimally invasive, nonendoscopic thyroidectomy (MINET) is a response to patients' requests for smaller incisions on the neck. In contrast to the traditional Kocher incision of 6 cm in the lower neck, the MINET incision is a 2.5-cm (1-in) incision that is made just caudal to the cricoid cartilage. This allows for control of structures at the superior pole. This operation is limited by the size of the thyroid neoplasm being excised. However, the incision can be easily extended to accommodate delivery of the thyroid mass.

Minimally Invasive Video-Assisted Thyroidectomy

This technique first described by Miccoli[53] and Bellantone[54] combines a traditional open thyroidectomy technique modified with a combined endoscopic approach. This is done without insufflation and uses blunt dissection. Briefly, a 30-degree, 5-mm diameter endoscope is introduced through a low (one fingerbreadth above the sternal notch) incision in the neck. Using external retractors, the superior pole vasculature is ligated under direct visualization.

Once the external branch of the superior laryngeal nerve, the superior parathyroid gland, and the RLNs are also visualized endoscopically and the superior pole is mobilized, the thyroid is retracted outside of the incision and the remaining portion of the operation is completed under direct vision. In a prospective randomized study, Miccoli reported that although cosmesis and postoperative pain were significantly better in MIVAT, conventional thyroidectomy still offers an advantage in terms of decreased operative time.[55] Patient selection plays an important role in this approach. Patient and tumor limitations include (1) thyroid nodule <3.5 cm; (2) absence of thyroiditis; (3) thyroid volume <15 mL; (4) cytologic and clinical evidence of benign disease, follicular tumor, or low-risk papillary carcinoma; and (5) absence of ultrasonographically enlarged lymph nodes in the neck.

Robotic Thyroidectomy

Robotic thyroidectomy represents a remote access thyroidectomy using the da Vinci robot. The published advantage of these approaches is improved cosmoses, although some suggest better visualization and magnification of the operative field and better surgeon ergonomics and dexterity with a robotic

approach.[56] The two robotic approaches described include a transaxillary approach and robotic facelift thyroidectomy (RFT). The largest experience with transaxillary thyroidectomy comes from Yonsei University, South Korea,[57–59] with some reports from the United States.[60,61] Robotic thyroidectomy using a gasless transaxillary approach eliminates the need for any cervical incisions. Experienced centers report excellent cosmetic results, decreased neck discomfort, and swallowing dysfunction.[59] Complications including stretch injury to the brachial plexus, perforation of the trachea, and injury to the carotid artery and internal jugular vein have been reported.[61] Lee et al.[62] reported on extending this approach to include patients with micropapillary carcinoma. Long-term oncologic follow-up is needed to fully assess the benefits of this approach.

An alternative remote access approach to the thyroid is the RFT, which uses a facelift incision in the postauricular area to provide entry to the thyroid compartment. This technique was developed with expectations that it would be less invasive and safer than the axillary-based approaches. In a small series, Terris compared transaxillary robot-assisted hemithyroidectomy versus RFT and reported a more rapid learning curve reflected by shorter operative times. Additionally, in the RFT arm, 9 of 10 patients were managed without a drain and in an outpatient setting, whereas all 5 of the transaxillary approaches were managed with drains as inpatients.[63] Certainly, long-term outcomes and large cohorts of patients have not been reported and are needed to fully assess the utility of this procedure.

Patient selection is critical with robotic thyroidectomy. Ideal patients are those with indeterminate, likely benign lesions <3 cm, where a unilateral lobectomy is indicated and body mass index <35 kg/m^2. Patients with inflammatory or previous neck surgeries should be considered poor candidates for remote access surgery as surgical planes may be difficult to dissect. Additionally, lesions located more deeply and posteriorly in the tracheoesophageal groove are more difficult to access with increased risk of injury to the trachea, esophagus, and RLN.

In summary, MIT offers patients an improved cosmetic outcome in the context of safely performed thyroid surgery by experienced surgeons. There is a significant learning curve associated with performance of these techniques and appropriate patient selection. Long-term outcome studies are

still needed especially with respect to oncologic outcomes.

MANAGEMENT OF LOCALLY ADVANCED THYROID CANCER

Surgical Management

Locally advanced thyroid cancer (LATC) is the result of direct extrathyroidal tumor extension (ETE) or extracapsular extension of involved lymph nodes into surrounding structures. As discussed above, gross ETE into surrounding structures is a poor prognostic indicator. The intricate relationship between the biology of the tumor, the risk of complete surgical resection at the expense of sacrificing vital structures, and the goals of the patient is essential in the management of LATC. The principles of surgical management of LATC are (1) removal of all gross tumor, (2) preservation of functioning structures, (3) preservation of vital structures, and (4) appropriate and selective use of adjuvant therapies. Structural imaging utilizing CT with contrast (Fig. 19.13) or MRI is essential in the preoperative evaluation of patients with ETE. Given the high association of ETE and distant metastases,[64] assessment for systemic disease should be undertaken before aggressive surgeries undertaken.

Figure 19.13. CT scan demonstrating LATC recurrence with airway invasion.

Invaded structures in LATC can be divided into central and laterally located structures. The most common structures invaded in the central neck include the strap muscles, RLN, trachea, laryngeal framework, esophagus, and pharyngeal constrictors.[65] Laterally, the carotid artery, internal jugular vein, vagus nerve, spinal accessory nerve, and phrenic nerve can be involved. Invasion of structures can occur in isolation or in combination with invasion of other involved structures. Discussion of structures invaded will be taken independently.

Recurrent Laryngeal Nerve Involvement

The findings of the preoperative evaluation of the vocal cords provide valuable information needed to make intraoperative decisions. Assessment of both the involved side of RLN and the contralateral nerve is important. Vocal cord paralysis is specific for RLN invasion; however, pressure can also result in impairment in vocal cord function.[66] In the clearest situation, a nerve that

is preoperatively paralyzed and found to be invaded at the time of surgery should be resected. Inability to remove all gross disease from the RLN is also an indication for resection. However, if vocal cord function is intact preoperatively, well-differentiated thyroid cancer can be peeled off the nerve cleanly during surgery if a gross total (R1) resection can be achieved. In nerves that function preoperatively, the Mayo Clinic and Japanese group have demonstrated that leaving microscopic disease on the RLN does not alter survival or local recurrence.[67,68]

For RLNs that are sacrificed, reanastomosis at time of surgery with the great auricular nerve, ansa cervicalis, or sural nerve has been shown to be effective in voice rehabilitation.[69,70] Early vocal fold medialization, especially in older patients with less ability to compensate, should be considered.

Laryngotracheal Invasion

A patient with LATC presenting with a fixed mass or less commonly hemoptysis should be evaluated for laryngotracheal invasion. Although tracheal invasion is the third most common site of invasion (after the strap muscles and RLN), direct laryngeal involvement is far rarer.[71]

Given the rarity of laryngeal involvement in LATC, cases should be considered on an individual basis. If the tumor can be shaved off of the laryngeal framework, this should be considered. For tumors invading laryngeal framework, resection of laryngeal cartilage or partial laryngectomy can be used. However, if the tumor is extending transluminal and invading the cricoid cartilage, total laryngectomy may be indicated.

Tracheal invasion is far more common than laryngeal invasion and therefore is more extensively studied and characterized. Shin et al.[72] described a staging system based on the depth of invasion (Fig. 19.14): Stage I cancer invades through the capsule of the thyroid gland and abuts but does not invade the external perichondrium of the trachea. Stage II cancer invades into the cartilage or causes cartilage destruction. Stage III cancer extends into the lamina propria of the tracheal mucosa with no elevation or penetration of the mucosa. Stage IV cancer is full-thickness invasion with expansion of the tracheal mucosa that is visible bronchoscopically as a bulge or an ulceration.

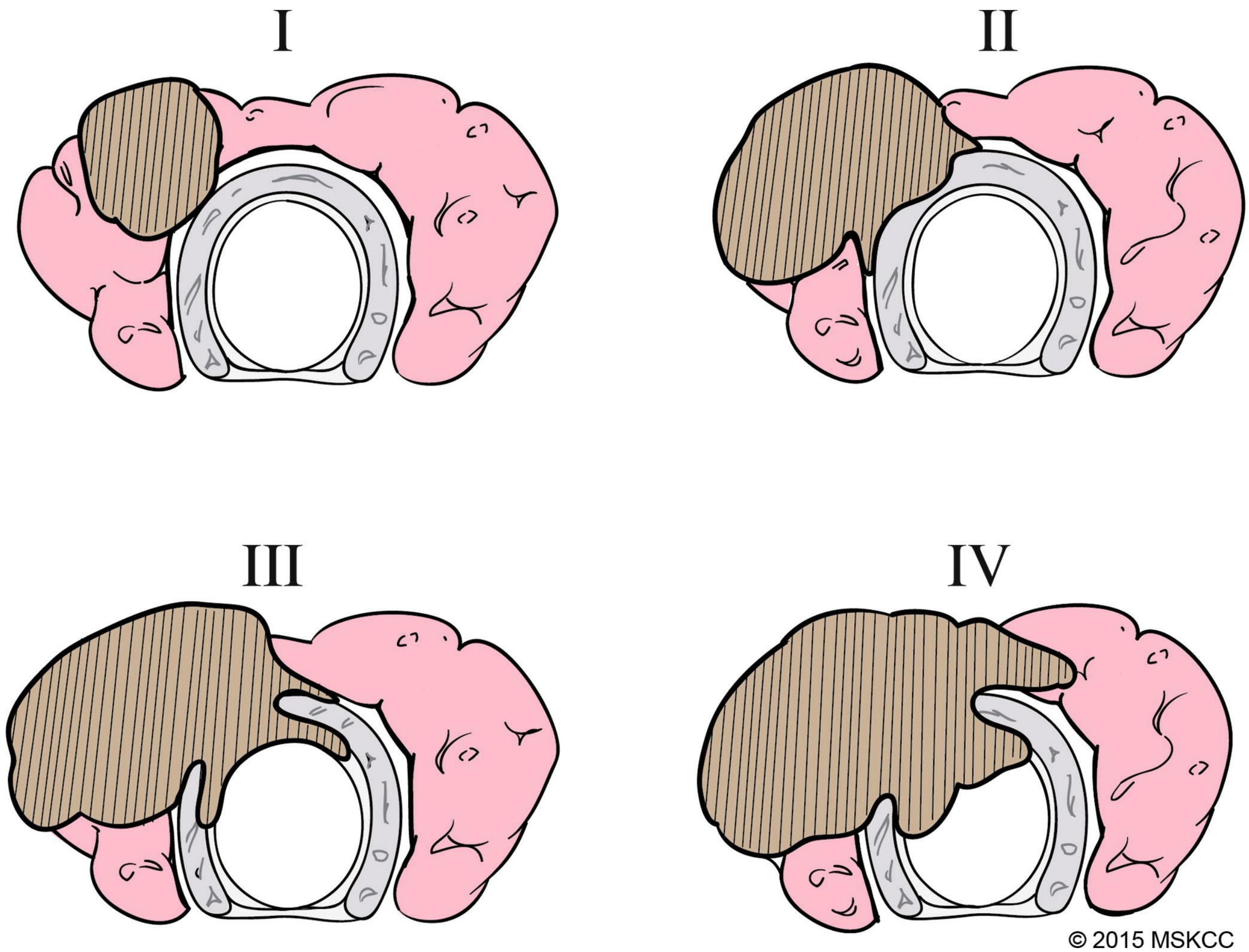

Figure 19.14. Tracheal invasion as described by Shin. Stage I invades through the capsule of the thyroid gland and abuts but does not invade the external perichondrium of the trachea. Stage II invades into the cartilage or causes cartilage destruction. Stage III extends into the lamina propria of the tracheal mucosa with no elevation or penetration of the mucosa. Stage IV is full-thickness invasion with expansion of the tracheal mucosa that is visible bronchoscopically as a bulge or an ulceration.

In the management of stage I tumors, although some have shown similar survival and local control rates when comparing shave procedures with more radical resection,[71] others have shown higher recurrence rates and worse survival.[73]

When conservative surgical management will most likely leave macroscopic disease behind on the trachea, more aggressive surgery is required. Options include window resection or wedge resection with primary closure or sternocleidomastoid muscle patch closure. When the tumor

involves more than one tracheal ring, sleeve resection and anastomosis should be undertaken. Resection of as many as seven to eight tracheal rings can be performed with primary anastomosis. In order to preserve blood supply, dissection should not extend 360 degrees of the trachea.

Esophageal Invasion

Direct extension via extracapsular spread from paratracheal or paraesophageal lymph nodes can result in invasion of the esophagus in one-fifth of patients with LATC and is a poor prognostic indicator.[71] Most commonly, the mucosa and submucosa layers are spared allowing an isolated resection of the muscularis layer resulting in a clear margin. However, in cases that require through and through resection, primary closure can often be achieved. An esophageal bougie or feeding tube placement can be helpful in identification of the esophageal lumen intraoperatively. Large defects may require reconstruction with local flaps or free tissue transfer.

Adjuvant Therapy

Patients with LATC have a higher rate of local recurrence, and completeness of surgical resection occasionally may not be achievable due to the extent of disease on presentation. In these cases, adjuvant therapy plays a significant role in the control of LATC. For patients with differentiated thyroid cancer that readily takes up iodine, RAI can be used for microscopic residual disease. In patients with gross residual disease, retrospective studies have shown external beam radiation therapy (EBRT) to be effective for local regional control.[74,75] Chow et al.[76] recommended adjuvant EBRT in patients with gross residual disease, positive resection margins, pT4, pN1b, or a lymph node size of >2 cm. The benefits of EBRT after adequately resected WDTC and in tumors with microscopic residual disease that readily take up iodine remain unclear. RAI scan results and PET scan results are useful in selecting patients most likely to benefit from RAI versus EBRT. Cytotoxic chemotherapy has shown little benefit in LATC. Overall, locoregional and progression-free survival (PFS) have been found to be equal for patients receiving EBRT versus EBRT plus chemotherapy. A benefit was observed in poorly differentiated histology; however, this was associated with a significantly worse distant metastasis-free survival.[77]

Targeted Therapy in Locally Advanced and Metastatic Thyroid Cancer

Over the past decade, we have observed significant advancement in the medical treatment of advanced thyroid cancer. Two multikinase inhibitors, levatinib[78] and sorafenib,[79] have been approved by the FDA for the treatment of patients with progressive, recurrent, or metastatic thyroid cancer that does not respond to treatment with radioactive iodine. Sorafenib was approved based on the phase 3 DECISION trial, which studied patients with recurrent and/or metastatic differentiated thyroid cancer and found that the median PFS was significantly longer in the sorafenib-treated group 10.8 months than in the placebo group 5.8 months.[79] The SELECT trial lead had similar inclusion criteria as the DECISION trial and led to the approval of lenvatinib. This trial demonstrated a median PFS in the treatment group of 18.3 months compared with 3.6 months in the placebo group with an overall objective response rate of 64.8%.[78] These drugs are hypothesized to exert their actions by targeting tumor angiogenesis by inhibiting vascular endothelial growth factor receptors VEGFR-1, VEGFR-2, and VEGFR-3. In addition, these agents also inhibit other kinases including RET, BRAF, and the platelet-derived growth factor receptor (PDGFR)-β in the case of sorafenib. In contrast, lenvatinib inhibits PDGFR-α, RET, the mast/stem cell growth factor receptor Kit, and the fibroblast growth factor receptors FGFR-1, FGFR-2, FGFR-3, and FGFR-4. These different kinase profiles may contribute to the differences in clinical efficacy observed in these two compounds. These drugs are associated with significant toxicity with 82% of patients requiring a dose interruption in the SELECT trial.[79] Quality of life and the long-term cumulative toxicities of therapy remain areas in need of further research. A comprehensive picture of how these systemic therapies benefit patients long term is still open to question.

MEDULLARY THYROID CANCER

Medullary thyroid cancer (MTC) was first described as the thyroid tumor that contained amyloid by Jacquet,[80] much later Hazard noted this as a histologically distinct thyroid carcinoma,[81] and it was then shown that this tumor originates from the neural crest–derived parafollicular C cells that

function and secrete polypeptide calcitonin.[82] It soon became clear that both sporadic and familial forms of MTC existed. The genetic forms exist as a component of the type 2 MEN syndromes MEN2A, MEN2B, and the related syndrome familial MTC (FMTC). Ten years after Takahashi et al.[83] discovered the rearranged during transfection (RET) oncogene in 1985, it was found that virtually all patients with MEN2A, MEN2B, and FMTC have RET germ-line mutations and ~50% of sporadic MTCs have somatic RET mutation.[84–86] The RET proto-oncogene is located on chromosome 10q11.2 and encodes a single-pass transmembrane receptor of the tyrosine kinase family that assists in cell trafficking, differentiation, and signal transduction.[87]Study of the RET proto-oncogene has added to the clinical understanding of the MTC, provided evidence for genetic counseling and prophylactic interventions, as well as opened the door for the utilization of targeted therapy. Common mutations are summarized in Table 19.9.

Table 19.9 Common Mutations in Medullary Thyroid Cancer

	Mutation	Exon	Phenotype	MTC Aggressiveness
Extracellular Cystein Rich Domain	533	8	FMTC	Moderate
	609	10	FMTC	Moderate
	611	10	FMTC/MEN2A	Moderate
	620	10	FMTC/MEN2A	Moderate
	630	11	FMTC	Moderate
	634	11	MEN2A	High
Intracellular Tyrosine Kinase Domain	768	13	FMTC	Moderate
	790	13	FMTC	Moderate
	804	14	FMTC	Moderate
	883	15	MEN2B	High
	891	15	FMTC	Moderate
	912	16	MEN2B	Moderate
	918	16	Men2B	Very High

Secretory Products of MTC and Their Clinical Utility

Parafollicular cells (C cells) comprise only 0.1% of thyroid cells that are scattered throughout the thyroid gland but are most numerous at the junction of the upper third and lower two-thirds of the gland. This accounts for the higher portion of MTCs located in the superior lobes. Parafollicular cells primarily secrete calcitonin, which acts to decrease blood calcium levels opposing the effects of parathyroid hormone (PTH). Other secretory products

include CEA, somatostatin, ACTH, vasoactive intestinal peptide (VIP), gastrin-releasing peptide, neurotensin, prostaglandins, and chromogranin. Patients with tumors secreting calcitonin and VIP can present with diarrhea and flushing. Cushingoid signs and symptoms can be observed in patients with tumors secreting ACTH.

Of these secretory products, calcitonin and CEA are valuable tumor markers in patients with MTC and can be useful for diagnosis, staging, and surveillance. Often, cytologic samples from MTC samples are difficult to distinguish based on the appearance of the cells alone. Higher accuracy has been reported with immunohistochemical staining for calcitonin or CEA in cases with suspected MTC.[88] Once the diagnosis of MTC is made, preoperative serum calcitonin levels have been correlated to tumor size and likelihood of surgical "biochemical cure." This correlation is more straightforward in familial and less correlative in sporadic cases.[89] In cases of nodal metastases, basal calcitonin levels can be in the range of 10 to 40 pg/mL (normal range <10 pg/mL), whereas distant metastases are typically associated with a calcitonin level >150 pg/mL and often >1,000 pg/mL. The ATA has incorporated preoperative calcitonin in deciding on the extent of surgical resection. In patients with MTC without distant metastases and no evidence of neck metastases on US, dissection of lymph nodes in the lateral compartments may be considered based on serum calcitonin levels.[90] However, although calcitonin levels are sensitive, a diagnosis of MTC cannot always be excluded by a normal preoperative calcitonin level.

Calcitonin levels play a significant role in prognosis and surveillance of patients postoperatively. Barbet et al. concluded that postoperative calcitonin doubling time (DT) is among the most powerful prognostic indicators in MTC. When calcitonin DT was <6 months, the 5- and 10-year survivals were 25% and 8%, respectively, whereas a calcitonin DT between 6 months and 2 years is associated with 5- and 10-year survivals of 92% and 37% and whereas all 41 patients with calcitonin DT >2 years were alive at the end of their study.[91] This clearly demonstrates the rapidity of rise in calcitonin levels can be used to aid in counseling and management of patients with MTC.

CEA is another useful tumor marker found in 50% of patients with MTC. Importantly, an increasing CEA level in the presence of a stable calcitonin level can be a sign of dedifferentiation of the tumor and is associated with a worse prognosis.

Incidence and Genetic Alterations in Sporadic and Hereditary MTC

MTC comprises 3% to 4% of all thyroid cancers. Most are sporadic accounting for about 75% of cases,[92] whereas the remaining coexists with hereditary syndromes including MEN2A and MEN2B syndromes or FMTC.

Sporadic MTC

The sporadic form of MTC comprises the majority of cases and most commonly presents a unifocal lesion later in life, most often in the fourth decade. Six to ten percent of patients with sporadic MTC harbor a de novo germ-line RET mutation.[93] Specific mutations have been shown to result in a more aggressive course. Specifically, somatic RET codon M918T mutation in sporadic MTC has been shown to have an aggressive clinical course and a poor prognosis.[94] However, overall sporadic MTC confers the best prognosis of all types of MTC.

Hereditary MTC

During the 1960s, Sipple noted an association between MTC, pheochromocytoma, and mucosal neuromas. Sipple syndrome (MEN2A) is inherited in an autosomal dominant fashion with the development of MTC reaching nearly 100% penetrance, usually before the age of 6 in a multifocal, bilateral pattern.[30] Fifty percent of patients with MEN2A will have an associated pheochromocytoma. Prior to surgery, pheochromocytoma should be excluded by measuring plasma or urine metanephrines.

MEN2B confers the worst prognosis of all types of MTC. Malignancies are multifocal, bilateral, and present extremely early in life, usually during infancy. MTCs develop with nearly 100% penetrance, and this syndrome also cares a 50% risk of pheochromocytoma. MTCs develop in infancy and are often multifocal and bilateral. In addition, MEN2B patients also have gastrointestinal mucosal ganglioneuromas and marfanoid body habitus.

FMTC denotes the best prognosis of the inherited MTC syndromes, and in contrast to MEN2 syndromes, it does not carry the risks of other clinical entities.[95] Like MEN2 syndromes, the MTCs associated with FMTC does present bilaterally in a multifocal pattern however is observed much later in

life, often in the third decade. A history of multiple family members presenting with MTC in isolation, later in life, helps distinguish MEN2A syndrome from FMTC.

Presentation of Patients with MTC

Age at presentation is often dependent on etiology. The typical age of presentation of sporadic MTC is in the fifth or sixth decade. In contrast, MEN2A and FMTC typically present in the third decade of life, and MEN2B usually presents in those younger than age 20. MTC patients will most often present with a palpable solitary thyroid nodule or thyroid mass. At the time of diagnosis, 70% of the patients will have cervical metastasis and 10% have distant metastases.[96] Presenting symptoms vary from asymptomatic to dysphagia or hoarseness secondary to RLN invasion. Systemic symptoms secondary to the functioning nature of these tumors are also common as discussed above. Diarrhea and flushing may be present, especially if calcitonin and/or VIP levels are elevated, and Cushingoid symptoms may be present if ACTH levels are elevated.

Management of MTC

Total thyroidectomy and dissection of cervical lymph node compartments, depending on serum calcitonin levels and US findings, are the standard treatments for patients with sporadic or hereditary MTC. Extent of lymph node dissection is controversial. Lymph node metastases are common. In patients with unilateral tumors, lymph node metastases have been observed in 81% of central node dissections, 81% of ipsilateral functional (level II to V) dissections, and 44% of contralateral neck dissection specimens. In bilateral tumors, the findings were similar. Importantly, these findings did not correlate to size.[97] Lymph node basins involved correlate with biochemical measures. Basal serum calcitonin levels exceeding 20 pg/mL, 50 pg/mL, 200 pg/mL, and 500 pg/mL were associated respectively with metastases to lymph nodes in the ipsilateral central and ipsilateral lateral neck, the contralateral lateral neck, and the upper mediastinum.[98]It is worth noting that the sensitivity of the surgeon’s intraoperative assessment for nodal metastases is 64%, with a specificity of 71%,[97] suggesting intraoperative assessment is not an optimal management plan in deciding extend of neck dissection.

The ATA has made recommendations on the extent of neck dissection that should be included in management of MTC in patients without distant disease.[90] Patients with no evidence of neck lymph node metastases by US examination should have a total thyroidectomy and dissection of the lymph nodes in the central compartment (level VI). Lateral compartments (level II to V) may be considered based on serum calcitonin levels. For patients with ipsilateral disease based on imaging, but negative in the contralateral neck compartment, contralateral neck dissection should be considered if the basal calcitonin level is >200 pg/mL.

It is essential to recognize the importance of parathyroid management in MTC. Patients with MEN2a can have parathyroid hyperplasia although it is often mild and often asymptomatic in comparison to MEN1.[99] The recommended treatment for primary hyperparathyroidism secondary to four-gland hyperplasia includes a subtotal parathyroidectomy leaving one gland, or a piece of one gland, in situ, or resection of only enlarged glands, with intraoperative PTH monitoring to document complete removal of hyperfunctioning parathyroid tissue. Ideally, this diagnosis should be made preoperatively.

Prophylactic Thyroidectomy

Prophylactic thyroidectomy is recommended in at-risk patients before the onset of clinically significant disease. A classic progression from C-cell hyperplasia to MTC to regional lymph node involvement and ultimately spread to distant sites is seen in patients with hereditary MTC. Timely thyroidectomy for MTC favorably alters the associated morbidity and mortality and the goal of prophylactic thyroidectomy is to intervene early in this progression. This should be balanced with the higher complication rates associated with thyroidectomy, the most significant being hypoparathyroidism in children compared to adults. This is less so in experienced hands. Therefore, the ATA has recommended that experienced physicians and surgeons in tertiary care centers should be responsible for the management of children with MEN2A or MEN2B. The age at which surgical management should be performed is dependent on mutational status.

Adjuvant Therapy in the Treatment of MTC

RAI therapy is ineffective in MTC. External beam radiation has not been studied in a prospective fashion and retrospective findings are often difficult to evaluate. Locoregional control is a valid endpoint in patients with MTC, as progression in the cervical region can have a significant impact on quality of life and survival. EBRT may improve locoregional control. 34 patients at high risk for MTC recurrence following thyroidectomy treated with a median total radiation dose of 60 Gy had a 5-year locoregional relapse-free survival rate of 87%. This would suggest some benefit of EBRT in locoregional control. It is important to note that R0 resection represents the best chance of locoregional control, however, but in patients with a high risk of recurrence due to positive margin, extrathyroidal extension, extensive lymph node metastases, or airway involvement, EBRT may be considered.

Systemic Therapy

Traditional single-agent chemotherapy has a low response rate in MTC. The most effective regimens are combination therapy with doxorubicin and another agent or 5FU and dacarbazine. Recent advances with targeted molecular therapies indicate that these agents may have benefit for patients with refractory disease.

Based on the results of two completed phase III clinical trials, the FDA approved two orally administered drugs vandetanib[100] and cabozantinib,[101] for the treatment of patients with advanced progressive MTC. Vandetanib targets the RET, EGFR, and VEGFR kinases. Partial responses were observed in 45% of patients treated with vandetanib, with a predicted median duration of response of 22 months. The improvement in quality of life, pain reduction, and diarrhea allowed a number of patients in the vandetanib arm to resume a normal social life. Responses were independent of RET mutation.[100]

Cabozantinib targets the kinases of RET, c-MET, and VEGFR. In the phase III trial, median PFS was significantly improved from 4.0 months (placebo) compared to 11.2 months (cabozantinib), and the overall response rate was 28%.[101]

Toxicity is not insignificant with the use of these two agents. Twelve percent of patients receiving vandetanib discontinued treatment due to toxicity and 35% required dose reductions because of an adverse event.[100]

For cabozantinib, 16% of patients receiving this agent discontinued treatment due to toxicity and 79% required dose reductions because of an adverse event.[101] Side effects included diarrhea, abdominal discomfort, fatigue, hypertension, and rash. Vandetanib was also associated with cardiac side effects specifically prolongation of the QTc interval.

Unanswered questions remain regarding the use of these agents. Resistance is observed over time, and toxicity remains and the issue of when to start and terminate these therapies are areas of ongoing debate and research.

ANAPLASTIC THYROID CANCER

ATC is a rare but highly lethal form of thyroid cancer. ATC patients have a median survival of 5 months and a 20% 1-year survival rate.[102] Patients with ATC will usually present with a rapidly enlarging neck mass often associated with symptoms consistent with invasion of surrounding structures including hoarseness and dysphagia. Risk factors for ATC are not well understood, but patients may have a history of goiter or prior coexisting differentiated thyroid cancer. It has been hypothesized that as the tumors dedifferentiate, more mutations develop, with ATCs commonly having multiple genetic abnormalities. Mutations in p53, BRAF, and Ras are common.[103]

Accurate histologic diagnosis of ATC is important in order to exclude other treatable entities with a better prognosis including PDTC and lymphoma. Although variable, a common morphologic presentation, and one that is most easily recognized as an anaplastic carcinoma of thyroid, is that of the biphasic spindle and giant cell tumor (Fig. 19.15). Other tumors are dominated by bizarre malignant giant cells, and still others may show a more pure population of spindle and squamoid cells. Tumors are highly proliferative with numerous mitotic figures and areas of necrosis.

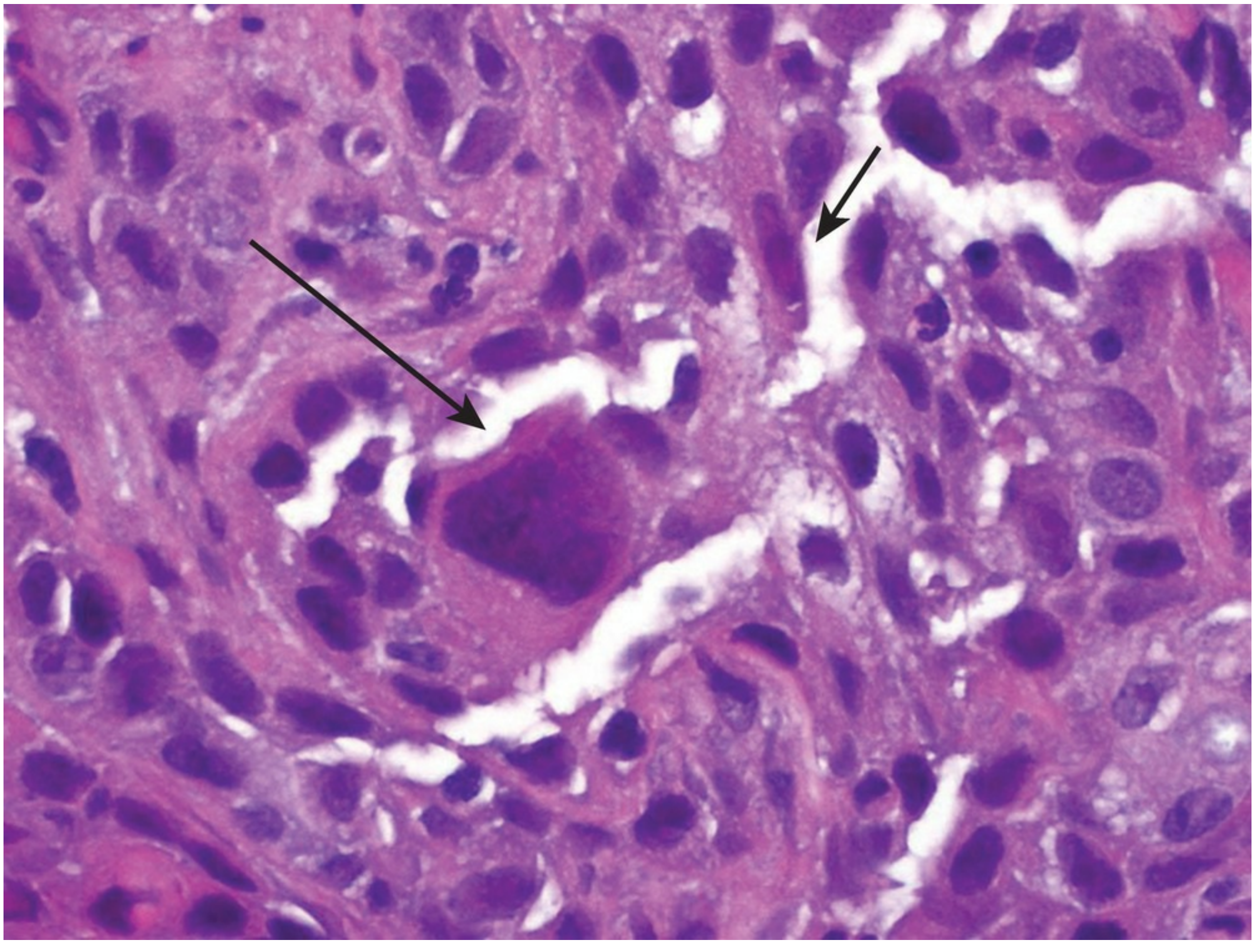

Figure 19.15. ATC with histologically characteristic giant cells (*long arrow*) and spindle cells (*short arrow*).

Management of ATC is challenging. Given the rapid progression of this disease, timely diagnosis and evaluation are essential. Once a diagnosis of ATC is made, a multidisciplinary team including a palliative care specialist should discuss the goals of care.

Patients with anaplastic thyroid carcinoma, resectable disease, and no distant metastases should be considered for surgical resection for better control of locoregional disease.

Goals of surgery must be clearly defined. If complete resection (R0/R1) can technically be achieved with minimal morbidity, it should be performed and may be associated with improved survival.[104] Importantly, gross tumor resection rather than debulking should be the goal of surgery. In patients with locoregional disease, the determination of whether the tumor is resectable should be based on what structures are involved, whether a satisfactory

resection can be achieved (R0/R1), and whether resection of the involved structure will result in significant morbidity or mortality. Surgery also plays a role in the management of ATC if the patients present in respiratory distress. Elective tracheostomy is best avoided unless there are acute airway issues. This has been an area of significant controversy. Although tracheostomy does prolong life, evading acute airway distress, and impending mortality, the chances of long-term survival are quite small in this patient population and there is question if the tracheostomy may prolong suffering. Certainly, this controversial area represents another challenge in treating patients with ATC.

Radiation is discussed in two patient populations with ATC. First is the surgically resected patient (R0/R1) receiving adjuvant radiation and the second is in the patient with unresectable ATC.

Selection bias certainly plays a role when analyzing treatment paradigms in ATC as patients presenting with less advanced/aggressive disease will often be the group offered therapy but a population in SEER-based study of 516 patients in a multivariate analysis revealed that, along with age, the combined uses of surgical resection and external beam radiotherapy were identified as the only independent predictors of survival.[105] In contrast, another group observed a survival benefit of 2 months with postoperative radiation that was not significant.[106] In patients with good performance status who wish to proceed with aggressive treatment, EBRT is offered with or without concurrent chemotherapy as soon as possible after surgery at our institution. Radiation with or without concurrent chemotherapy is also offered in patients who have undergone R2 resection or have unresectable disease with good performance status and who wish an aggressive approach. Radiation can also be used to palliate local symptoms.

Cytotoxic chemotherapy involving some combination of a taxane (paclitaxel or docetaxel) and/or anthracyclines (doxorubicin) and/or platin (cisplatin or carboplatin) can be given concurrently with radiation in patients who wish to proceed with aggressive management.

SUMMARY AND CONCLUSIONS

Thyroid cancer is the cancer with the most rapid increase in incidence worldwide. The incidence of thyroid cancer has almost quadrupled in the last quarter of the century, but fortunately, the vast majority of these tumors are

well-differentiated microcarcinomas with overall survival approaching 98%. There have been several new advances in the diagnostic evaluation of thyroid cancer including genetic expression classifiers and molecular analyses of needle biopsies. These are ancillary tests that help make a decision that thyroid nodules have a high index of suspicion for cancer and need to be operated on. The debate continues regarding the extent of thyroidectomy and lobectomy versus total thyroidectomy in early-stage disease. Another debate now revolves around the role of prophylactic central compartment dissection and extent of lateral neck dissection recommended in the treatment of early- to intermediate-risk tumors. The role of radioactive iodine continues to evolve with less and less use of radioactive iodine in patients with low-risk thyroid cancer. If RAI is to be used, it is best used now with recombinant TSH rather than making patients hypothyroid for 6 to 8 weeks. This is a major advance in maintaining the quality of life of these patients with thyroid cancer. Posttreatment tumor surveillance is based on serum thyroglobulin assay and ultrasound of the thyroid. PET scan plays an important role in aggressive thyroid cancers such as tall cell or poorly differentiated thyroid cancer. The role of external radiation therapy continues to evolve as we understand more about the prognostic factors of thyroid cancer and aggressive histologies. Ultrasound has become an important diagnostic tool both preoperatively and postoperatively for long-term follow-up. Genetic evaluation of patients presented with MTC is extremely critical especially with respect to RET mutation as this test plays an important role when considering prophylactic thyroidectomy in children with MTC and RET mutation. Calcitonin DT and thyroglobulin DT are also important prognostic markers in the management of MTC patients. There is considerable interest in nerve monitor and energy devices such as harmonic and LigaSure during the procedure of thyroidectomy. Remote access thyroid surgery appears to be quite popular in Southeast Asia with debatable interest in the United States. Anaplastic thyroid carcinoma continues to be a major treatment challenge to the treating physicians and it appears that we have made very little progress in the management of this nearly universally lethal disease. However, combination chemotherapy, external radiation therapy, and targeted therapies have enabled us to offer the best treatment available today.

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20 Tumors of the Parathyroid Gland

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The parathyroid glands maintain a delicate calcium homeostasis within the body, and dysfunction of these glands may result in significant sequelae. The recognition and treatment of parathyroid disorders can be challenging. Modern advances in imaging techniques and intraoperative parathyroid hormone (PTH) assays are invaluable in the contemporary management of parathyroid disorders.

HISTORY

The history of the parathyroid glands, from their discovery to the understanding of their physiologic and pathologic importance, unfolded somewhat recently. In November of 1849, the two-ton great Indian Rhinoceros owned by the Zoological Society of London passed away. Sir Richard Owen, a renowned British anatomist and Conservator of the Museum in the Royal College of Surgeons, dissected the cadaver in his own resident quarters.[1,2] He provided the first recorded description of the parathyroid gland: “a small compact yellow glandular body attached to the thyroid at the point where the vein emerged.”[1]

In 1880, a Swedish medical student Ivar Viktor Sandström identified a vascularized organ distinct from the thyroid gland and lymph nodes that he named *glandulae parathyroidae*.[1–3] In his writings, Sandström even noted the variable location of these entities.[3]

It was not until the work of French physiologist Eugene Gley some years later that the function of these structures became evident.[1] Tetany was first described following thyroidectomy cases performed by Bilroth in the late 1870s. Initially, this complication was attributed to hyperemia of the brain as

a result of the thyroidectomy.[3] Gley observed that tetany and death ensued if these *glandulae parathyroidae* were excised during thyroidectomy in dogs. Further studies revealed that the abnormal neuromuscular sequelae seen in animals postthyroidectomy could be prevented by autotransplantation of these glands.[1]

In 1891, Friedrich Daniel von Recklinghausen described lesions that he termed osteitis fibrosa cystica of von Recklinghausen.[1,2] A Viennese pathologist, Jakob Erdheim, also found enlarged parathyroid glands on autopsy of patients with osteomalacia and osteitis fibrosa cystica.[3] At that time, the bone disease was not attributed to a parathyroid abnormality; in fact, parathyroid enlargement was believed to be a compensatory consequence of the bone disease.[1–3] In 1915, another Viennese pathologist, Friedrich Schlagenhaufer, described two patients with osteomalacia who were each found to have a single parathyroid tumor at autopsy, suggesting that the enlarged parathyroid glands might actually be the cause of the bone disease.[1]

It was not until 10 years later that Felix Mandl, a Viennese surgeon, attempted the first excision of a parathyroid tumor in a patient with severe von Recklinghausen disease. The patient, a tram conductor, was severely disabled and unable to ambulate due to his disease.[1,2] He underwent a neck exploration with excision of a 25-mm “yellowish-brown almond-shaped tumor” in the area of the left inferior thyroid gland. A few days postoperatively, the patient was able to walk without assistance and demonstrated significantly lower blood and urine calcium levels. He did well for 6 years before experiencing recurrent hypercalcemia and nephrolithiasis. Upon reoperation, Mandl was unable to find abnormal parathyroid tissue, and the patient passed away shortly thereafter. The recurrence was attributed to ectopic parathyroid tissue, but, interestingly, none was found at autopsy.[1,2]

The first parathyroid operation in the United States followed shortly thereafter. The patient, sea captain Charles Martel, was diagnosed with hyperparathyroidism (HPT) and had lost 6 inches in height due to associated bone demineralization.[2,3] He underwent six operations, beginning in 1927, at the Massachusetts General Hospital that either removed normal parathyroid tissue or found no abnormal tissue. By 1932, his renal function had begun to deteriorate and Dr. Churchill, under the insistence of Martel himself, planned a mediastinal exploration to search for ectopic parathyroid tissue. A 3-cm

tumor was identified in the mediastinum and removed. Unfortunately, the patient developed an impacted ureteral stone several weeks later and passed away from laryngospasm during a procedure to relieve the obstruction.[2] The first documented parathyroid carcinoma was excised at Cook County Hospital in Chicago in 1926. The patient, a 29-year-old female, had multiple masses in the neck and required multiple subsequent excisions for recurrences.[3]

In 1963, Berson and Yalow developed a radioimmunoassay for PTH that allowed for the accurate acquisition of serum PTH levels.[2–4] The development of multichannel autoanalyzing systems made it possible to rapidly determine serum calcium levels. With the advent and subsequent improvement of these innovations, asymptomatic patients could be diagnosed with parathyroid abnormalities before presenting with advanced bone and renal disease, allowing for more expeditious and efficacious management.

EMBRYOLOGY AND ANATOMY

During the 5th week of gestation, the inferior and superior parathyroid glands develop from the dorsal endoderm of the third and fourth branchial pouches, respectively.[2,4,5] As the cervical spine lengthens and the heart and great vessels descend, the inferior glands migrate caudally within the tail of the thymus. As the thymus migrates further into the upper thorax, its tail involutes, leaving the inferior glands near the inferior poles of the thyroid gland.[2,4,5] Concurrently, the superior glands migrate intimately associated with the ultimobranchial bodies, halting at the lateral aspect of the posterior superior to the middle third of the thyroid gland. This disparity in migrational distance during development explains the increased variability of anatomic locations of the inferior parathyroid glands as compared to those of the superior glands.[5] Ectopic parathyroid glands have a reported incidence ranging from 6% to 19%.[6,7]

Most individuals have four parathyroid glands. Fewer than four glands have been found in ~2% to 3% of individuals.[8–11] The incidence of supernumerary glands ranges from 5% to 13%.[5,8,9] Dissection of 428 cadavers by Gilmour[12] in 1928 revealed 5 parathyroid glands in 6.7% of the specimen, 6 in 0.05% of the specimen, and 12 parathyroid glands in one

specimen. Supernumerary glands are commonly found in the mediastinum within the thymus or associated with the thyrothymic tract.[2] Surgeons must be cognizant of the potential variability in the number of parathyroid glands, particularly in patients with multigland disease. In one study of over 2,000 patients who underwent surgery for primary HPT, the offending parathyroid adenoma was found to be a supernumerary gland in 0.7% of the cases.[13]

The superior parathyroid glands lie dorsal to the coronal plane created by the course of the recurrent laryngeal nerve (RLN) through the neck; the inferior glands lie ventral to this plane.[5] This relationship to the plane of the RLN is nearly always constant and therefore an important concept during surgical exploration of the glands.

In approximately 80% of patients, the superior parathyroid glands can be identified within 1 cm above the intersection of the RLN and inferior thyroid artery. They are usually intimately associated with the thyroid capsule at the posterosuperior thyroid pole.[2,5] The glands can be distinguished from neighboring thyroid nodules by their mobility within the extension of the pretracheal fascia that also envelopes the thyroid gland.[2] Common locations of ectopic superior parathyroid glands include paraesophageal, retroesophageal, and retrolaryngeal sites; the tracheoesophageal groove; within the thyroid gland; the posterior mediastinum; and within the carotid sheath.[5,7,14] In rare instances, they are found in lateropharyngeal or intercricothyroid and retropharyngeal locations.[2] In some instances, the superior glands may be overly descended, lying inferior to the inferior parathyroid glands; alternately, they may also be found in an undescended location near the hyoid bone or pharyngeal musculature.[4]

The inferior parathyroid glands are generally found on the posterolateral aspect of the lower thyroid pole, inferior to the intersection of the RLN and inferior thyroid artery. They may also be found within the thyrothymic ligament.[7,15] As mentioned previously, due to its longer course of migration during development, the inferior glands have more variability in anatomic position than the superior glands.[5] Additionally, if there is a delay or failure to separate from the thymus, the inferior glands may be drawn into the anterior mediastinum.[5] Common ectopic locations include the thyrothymic ligament and anterior mediastinal, intrathymic, and intrathyroidal positions.[5] Less common ectopic sites include the aortopulmonary window, the carotid

sheath, and pericardial and pyriform sinus locations.[2,7]

Acquired ectopia of enlarged neoplastic and normal parathyroid glands results from migration under the influence of gravity, changes in intrathoracic pressure, deglutition, and mechanical mass effect as in the case of large goiters. In such instances, superior parathyroid glands can migrate along the posterior vertebral fascia into the posterosuperior mediastinum.[2,7,16] Similarly, the inferior glands can migrate into the anterior mediastinum along the thyrothymic ligament.[5] It is estimated that up to one-third of missed parathyroid adenomas are ultimately located in the anterior mediastinum.[2]

With some variability, the superior glands derive their blood supply from a single branch off of the inferior thyroid artery. Occasionally, the arterial supply is from a branch of the superior thyroid artery or from an arterial anastomoses.[2,5] Venous drainage is usually via the superior or lateral thyroid veins. The inferior thyroid artery also supplies the inferior parathyroid glands; this relationship is often retained even in cases of ectopic mediastinal migration, but rare cases of arterial supply from a branch of the internal mammary artery or a direct branch off the aortic arch have been reported.[5,15] Venous drainage is often via the lateral or inferior thyroid veins.[5] Lymphatic drainage of the parathyroid glands parallels that of the thyroid gland, draining into the paratracheal and deep cervical lymphatic nodes.[2] Preservation of the vascular supply during surgery is crucial in maintaining the viability and function of the gland.

Normal parathyroid glands are smooth with an oval or bean shape. They typically weigh between 40 and 50 mg, though some studies have cited the upper limit of normal to be 65 mg.[2,5] Variations in weight have been observed between ethnicities, genders, comorbidities, and even within individuals. Contingent upon vascularity, adipose tissue, and oxyphil content, their color ranges from tan to reddish brown.[2,4] Parathyroid glands can easily be confused with adipose tissue, thyroid nodules, lymph nodes, or thymic remnant. They may be distinguished from adipose tissue by a characteristic “gliding” motion against the surrounding tissues. Careful visual observation and subtle differences in palpation can distinguish between a normal and abnormal gland.

Histologically, a thin connective tissue capsule is present with septae extending into the parenchyma, dividing the gland into clusters of functional

cells. The parenchyma is predominantly composed of chief cells residing in an adipose tissue–rich stroma. The functional chief cells are slightly eosinophilic and contain copious PTH secretory granules. The percentage of adipose tissue content in normal glands, previously thought to be a marker of functional status, has been seen to vary among individuals depending on age, gender, and possibly other factors.[2] Oxyphil cells contain an abundance of mitochondria. Although their function is unknown, some theorize that their high mitochondrial content may explain the high avidity of abnormal parathyroid glands for the technetium (Tc)-99m used in localization scans.[2]

PHYSIOLOGY

PTH is an essential factor in the intricate balance of serum calcium homeostasis. PTH secretion is primarily in response to low serum ionized calcium levels, the active component of serum calcium. This is a sensitive relationship; even minute alterations in calcium concentration by as little as 0.04 mmol/L have been shown to elevate serum PTH by 100% or more.[2] Its influence is exerted via cyclic adenosine monophosphate (cAMP) pathways on bone to increase osteoclastic reabsorption and on the kidneys to increase tubular calcium absorption, decrease calcium excretion, and increase tubular phosphate excretion. Additionally, PTH promotes renal 1α-hydroxylase–mediated conversion of 25-hydroxyvitamin D3 (calcifediol) to 1,25-dihydroxyvitamin D3 (calcitriol). This biologically active form of vitamin D, in turn, stimulates the small intestine to increase absorption of calcium and phosphorus. Calcitriol also promotes the release of calcium and phosphate from bone. The net effect is an increase in serum calcium and a drop in serum phosphate. The increase in serum calcium produces negative feedback to decrease the secretion of PTH (Fig. 20.1). As a further feedback mechanism, if calcium levels are too high, calcitonin, produced by parafollicular C cells of the thyroid gland, inhibits calcium reabsorption from bone and increases renal clearance of calcium and phosphate.[2,5,17]

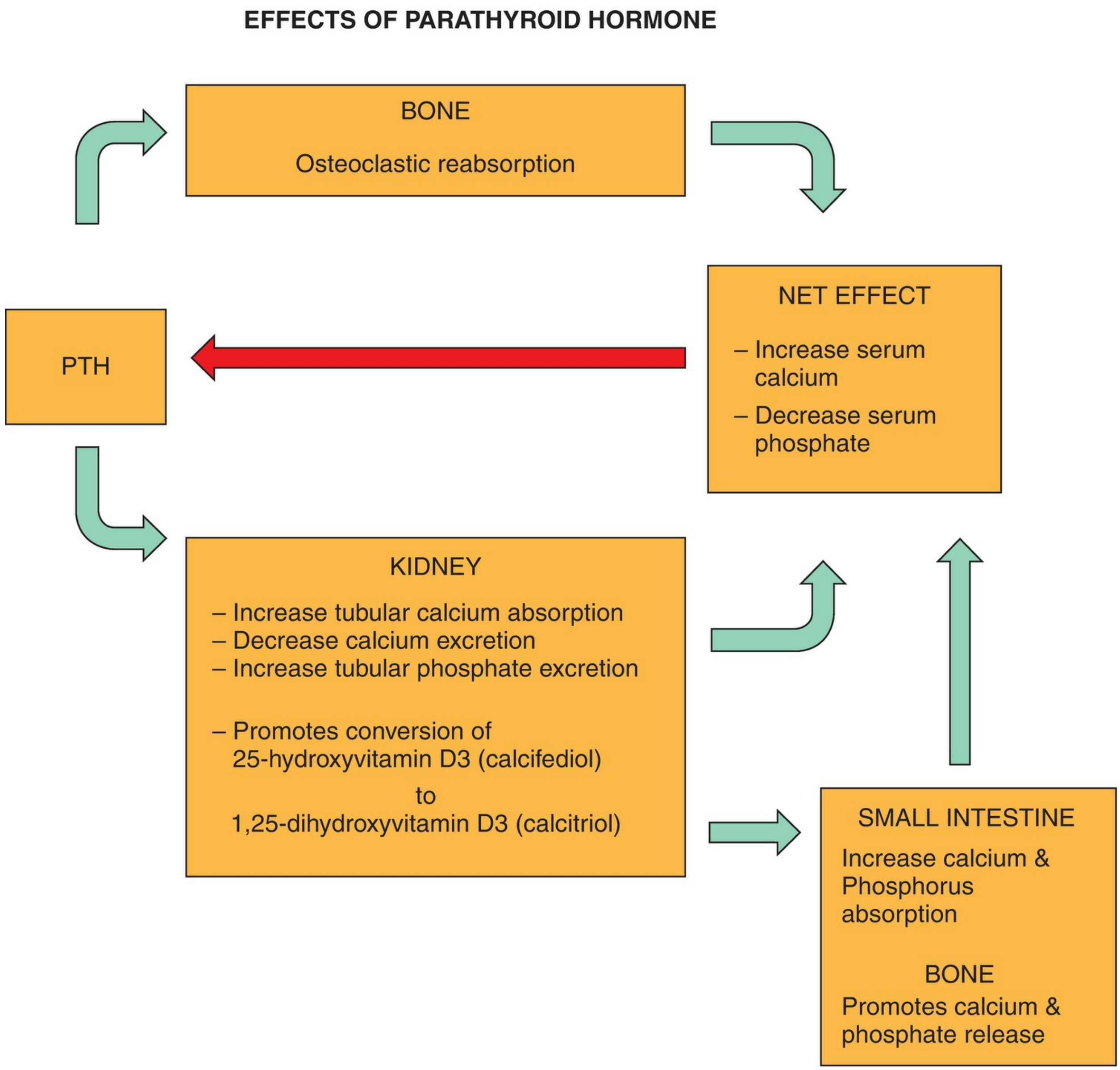


Figure 20.1. Effects of parathyroid hormone (PTH).

Once secreted from the parathyroid gland, the biologically active (1 to 84) PTH molecule is rapidly degraded, with a half-life of 3 to 5 minutes in individuals with normal renal function. The intact form is cleaved into a biologically active amino-terminal fragment that is rapidly cleared from the circulation and an inactive carboxyl-terminal fragment that undergoes slow renal clearance.[2,17] The initial PTH radioimmunoassays took up to 24 hours to obtain results. With the development of immunoradiometric assays and subsequent immunochemiluminometric assays (which utilize distinct antibodies for the amino and carboxyl terminals of the intact PTH molecule),

the process can be reduced to <15 minutes. Newer assays that measure the intact hormone are a more accurate measure as compared to older assays that principally measured the inactive fraction.[2,17] Such assays can be used for rapid intraoperative assessments of PTH levels. Recent studies have found that some assays may utilize antibodies that cross-react with fragments they were not intended to target. This may hold especially true for patients with renal failure and may account for some of the variability between different assays types.[17]

Of note, nonparathyroid sources of PTH have been reported in rare cases of malignancy including ovarian, small cell carcinomas, and neuroendocrine tumors.[2,18]

BENIGN LESIONS

Parathyroid Adenoma

Parathyroid adenomas are benign tumors of the parathyroid gland and account for 80% to 90% of primary cases of HPT.[2,5] Parathyroid adenomas have a female predominance with an increased incidence in individuals over the age of 50. An association between head and neck ionizing radiation exposure at an early age and development of parathyroid adenomas has also been shown.[19,20] The majority of adenomas occur sporadically and usually involve a solitary gland. Some sources indicate inferior gland involvement more frequently than the superior glands.[2,5,21] The incidence of multiple adenomas has been reported to range from 1.7% to 11.5%.[22,23]

Parathyroid adenomas are monoclonal neoplasms composed of a clonal expansion of cells with altered calcium sensitivity.[22,24] Various genomic events have been proposed as the trigger for this cellular propagation. Among the events recognized are a rearrangement of protooncogene *parathyroid adenomatosis 1* (PRAD1) into the vicinity of the regulatory region responsible for PTH synthesis.[25,26] Somatic mutations of the *multiple endocrine neoplasia 1* (MEN1) tumor suppressor gene have been demonstrated in 20% of primary HPT cases.[27] The loss of tumor suppressor function, specifically of loci, located on chromosome 1p, is believed to be an even more common cause of sporadic adenomas.[28]

Upon gross examination, parathyroid adenomas tend to have a more reddish-brown coloration and an increased, rubbery consistency as compared to normal glands. Adenomatous glands may be bi- or multilobed with a smooth, nodular, or cystic-appearing capsule.[2] Histologic examination reveals hypercellular nodules of chief cells arranged in sheets or cords surrounded by a rim of normal-appearing parathyroid tissue. Compared with those contained in normal glands, chief cells within adenomas are larger with more nuclear pleomorphism and giant cell formation. Nuclear atypia and mitotic figures may also be observed, but these characteristics are not of diagnostic value in distinguishing between benign or malignant parathyroid abnormalities.[2,5,29]

Various subtypes of parathyroid adenomas have been reported, including oncocytic adenomas, lipoadenomas, water-clear cell adenomas, large clear cell adenomas, and atypical adenomas. Most have previously been thought to be nonfunctioning entities; however, recent evidence may suggest associations with HPT.[2]

Hyperplasia

Primary chief cell hyperplasia causes enlargement of all parathyroid glands either uniformly or variably and accounts for 5% to 15% of primary HPT cases. As with parathyroid adenomas, hyperplasia also shows a female predilection.[2,5] It is characterized by a proliferation of chief cells, and sometimes oncocytes, in multiple glands, causing an increase in parenchymal bulk without a known stimulus for elevated PTH secretion. The parenchymal cells can form solid sheets, cords, or follicles.[5] Nuclear atypia and mitotic figures are very rarely seen.[2] Hyperplastic glands lack the “rim” of normal parathyroid tissue found in adenomas, but a “pseudorim” around nodules may be seen within the hyperplastic glands.[5] Approximately 30% of cases are associated with some type of familial HPT or MEN syndrome.[2]

A rare form of hyperplasia, water-clear cell hyperplasia, can cause significant hypercalcemia. Interestingly, this is the only condition where the superior parathyroid glands are consistently larger than the inferior glands. Glands affected by this hyperplasia are often asymmetrically enlarged with lobular extensions and have a dark chocolate brown color. Microscopically, there is a diffuse proliferation of clear cells with small dense nuclei and

cytoplasm filled with small vacuoles.[2,5] Histologically, the appearance is similar to that of renal cell carcinoma.[2]

In cases of hyperplasia secondary to renal failure, the glands appear to be more uniform in size early in the disease. Asymmetry becomes more pronounced as the disease progresses, and the degree of enlargement seems to mirror the severity of renal disease.[2]

Multigland Disease

The incidence of synchronous double parathyroid adenomas ranges from 2% to 10% and increases with age. It is estimated that ~50% of double adenomas localize to two distinct locations on preoperative studies.[2] Intraoperative PTH assessment can be extremely helpful in reflecting the sequential decrease in hormone levels after excision of each hyperfunctional gland. Identification of at least one normal gland is crucial in ruling out four-gland hyperplasia.

In approximately 10% to 15% of patients with sporadic primary HPT, diffuse hyperplasia of the parathyroid glands may be present.[2] A thorough medical and family history must be performed to rule out MEN syndrome. Preoperative localization studies may not localize in these cases. Bilateral exploration should be performed if this condition is suspected. Intraoperative PTH levels are useful to confirm that all hyperfunctional tissues have been removed.

MALIGNANT LESIONS

Parathyroid Carcinoma

Parathyroid carcinoma is a rare malignancy and accounts for <1% of cases of primary HPT. In contrast to the previously mentioned etiologies of primary HPT, there is equal gender distribution, and this condition often presents during the fourth through fifth decades, ~10 years younger than patients with benign primary HPT. There is no apparent ethnic or geographic predominance.[5,30,31] Purported association with history of head and neck irradiation, chronic renal failure, and familial HPT, in particular familial isolated HPT and hereditary hyperparathyroidism–jaw tumor syndrome (HPT-JT) and MEN syndromes, has been reported.[30,32–34] Overexpression of

cyclin D1 has been found in a high percentage of parathyroid carcinomas, but the significance of that finding is unknown. An inactivating mutation of a recently described tumor suppressor gene *HRPT2* that encodes for the protein parafibromin, a protein with unknown function, has been identified as a possible factor in the pathogenesis of parathyroid carcinomas.[30,35]

Parathyroid carcinomas have been identified in eutopic, ectopic, and supernumerary glands.[36] In contrast to patients with benign causes of primary HPT who generally present with mild hypercalcemia, patients with parathyroid carcinomas can present with significantly elevated calcium levels that are 3 to 4 mg/dL above the upper limit of normal.[5,30] Approximately 70% of patients present with serum calcium levels above 14 mg/dL and intact PTH levels at least five times the upper limit of normal. Additionally, a palpable firm cervical mass is noted in 30% to 50% of patients upon presentation.[2,37] Eighty percent of patients complain of hypercalcemic symptoms including fatigue, weakness, and polydipsia, and many manifest evidence of target organ effects, specifically within the kidney and skeletal system. One series reported nephrolithiasis in 56% and renal insufficiency in 84% of patients with parathyroid carcinoma; another cited concomitant bone and renal disease in 50%.[30,31,37] This is in contrast to patients with benign causes of HPT where only about half complain of symptoms and neck masses are very rarely seen.[30] The finding of RLN palsy should also heighten suspicion for carcinoma.[2,5,38]

Definitive preoperative diagnosis is impossible. Biopsy is not recommended due to the possibility of tumor seeding.[5] Treatment consists of an en bloc wide resection with a tumor-free margin of tissue, central neck dissection, and ipsilateral thyroidectomy.[2,39] If local infiltration into surrounding structures including the strap muscles, RLN, trachea, or esophagus is found, excision is required to reduce risk of recurrence. Regional metastases to the lateral cervical nodal basins and distant spread to the lungs, liver, kidney, and bone can also be seen. If local or metastatic spread is evident, a wide resection of the metastases is indicated with the aim of reducing tumor burden and thereby serum calcium levels. Metastatic cancer to lateral cervical neck basins is rarely encountered during the initial presentation; thus, lateral neck dissections should be performed only for clinically or radiographically identifiable lymphadenopathy.[2,40]

Some investigators have also advocated for the use of postoperative adjuvant radiotherapy in select cases to reduce the rate of locoregional recurrence.[41–45] One recent series followed 27 patients treated at MD Anderson and reported that the rate of local recurrence appeared to be lower in patients who received adjuvant radiotherapy.[44] To date, studies have followed small patient cohorts without comparison groups, so quantitative significance remains unclear.[43,46] The context of disease, such as extent of disease, positive margins, and angioinvasion, in which adjuvant radiotherapy may be indicated still remains to be defined.[47] The efficacy of other treatment modalities including chemotherapy, bisphosphonates, and biotherapy has also not yet been proven.[2,48]

Parathyroid carcinomas are considered a slow-growing disease in most cases. Morbidity and mortality are secondary not to tumor spread but rather to the effects of severe hypercalcemia. The overall 5- and 10-year survival rates are estimated to be 77% and 63%, respectively.[5] Appropriately aggressive surgical resection during the initial operation is considered one of the most crucial prognostic factors for parathyroid carcinoma.[2,31] Although cure is rare in cases of recurrent cancer, which may present up to 20 years or more after initial treatment, every effort to perform reoperations should be undertaken to reduce the tumor burden and the associated hypercalcemia.[2,5]

Grossly, parathyroid carcinomas are firm, grayish-white masses with increased vascularity and are often found to be densely adherent to surrounding soft tissues. As frozen section is unreliable, diagnosis is made histologically based on presence of capsular and vascular invasion. Mitoses can be an indicator of malignancy, but as mentioned previously, mitoses may also be identified in cases of parathyroid adenoma or hyperplasia; furthermore, the absence of mitotic figures does not exclude the diagnosis of carcinoma.[49] Desmoplastic reaction, nuclear atypia, and necrosis may also be more common in carcinoma than in benign lesions but also do not constitute a diagnosis. It is also unclear if parathyroid carcinoma arises from malignant transformation of an existing benign lesion.[2]

HYPERPARATHYROIDISM

Primary Hyperparathyroidism

Primary HPT is a disorder of excess PTH production by one or more parathyroid glands with subsequent serum calcium level elevation. Primary HPT should also be considered in cases where the PTH level is within the normal range but is inadequately suppressed relative to the serum calcium level. The disease is three times more common in women and typically presents during the sixth decade. The prevalence of primary HPT in the general population is 0.1% to 0.3% but is 1% or higher in women over 60 years of age.[2] Wermers et al.[50] determined from a population-based study from 1993 to 2001 that a significant spike in the diagnosis of primary HPT in the 1970s, attributable to the widespread use of automated serum calcium measurements, gave way to a progressive decrease in incidence. Theories for this decline include an increase in supplemental calcium and vitamin D use, the use of head and neck irradiation for various benign childhood disorders becoming obsolete, and the removal of serum calcium levels from routine chemistry panels at that institution. Parathyroid adenomas are responsible for 80% to 90% of primary HPT cases, and the majority of those are from single-gland disease. Approximately 5% to 15% are due to parathyroid hyperplasia and <1% are due to parathyroid carcinoma.[2,5,22,51]

Secondary Hyperparathyroidism

Secondary HPT is caused by an external stimulus, usually chronic renal failure, which induces a disruption in calcium homeostasis. This results in elevated serum PTH levels in the setting of hypocalcemia. Other etiologies include osteogenesis imperfecta, Paget disease, multiple myeloma, pituitary adenoma, and conditions that cause vitamin D deficiency.[2,52]

In chronic renal failure, the kidneys are unable to excrete phosphorus, reabsorb calcium, or produce adequate levels of calcitriol. Consequently, serum calcium levels decrease, providing stimulus to the parathyroid glands. Hyperphosphatemia can also directly stimulate PTH synthesis while indirectly decreasing the free calcium level.[2,5] Chronic HPT in patients with renal failure can lead to bone disease including osteitis fibrosa cystica and mixed uremic osteodystrophy. Other consequences like neurobehavioral changes and soft tissue calcification, including that of the cardiovascular system, can also be seen.[52,53] In fact, coronary artery calcifications have been shown to be more common in younger patients on dialysis.[54]

The first-line treatment is correction of the underlying cause and medical therapy. Surgery is usually considered in cases refractory to medical therapy and in cases of severe hypercalcemia, severe bone disease, calciphylaxis, severe pruritus, or severe myopathy. PTH levels are usually >1,000 pg/mL.[52] There are no firm National Institutes of Health (NIH) guidelines for surgery as there are for primary HPT, but recent studies have supported surgical treatment in improving the symptoms and quality of life in patients with secondary HPT.[55] Percutaneous ethanol injection therapy (PEIT), first introduced in the 1980s but used sporadically due to its technical difficulty, has been recommended by groups in Japan as an alternative to surgical therapy in select cases.[56]

Tertiary Hyperparathyroidism

Tertiary HPT is characterized by autonomous overproduction of PTH from the parathyroid glands following long-standing secondary HPT that persists after the inciting stimulus has been rectified. This state is no longer influenced by serum calcium levels. Persistently elevated serum PTH levels in the setting of hypercalcemia and low phosphorus levels are seen after renal transplantation. In this condition, correction of the underlying etiology, for instance, successful renal transplantation in chronic renal failure patients, does not halt the excess production of PTH. Etiologies besides chronic renal failure causing tertiary HPT are rare.[5,52]

Most cases demonstrate hyperfunction of all the parathyroid glands; thus, a total or subtotal parathyroidectomy is recommended. As in secondary HPT, there are no NIH guidelines for surgery. The exact mechanism of tertiary HPT is yet unknown but is theorized to be due to the monoclonal expansion of parathyroid cells forming nodules within already hyperplastic glands and a shift in the set point of the calcium-sensing mechanism.[2,52]

Familial Causes of Hyperparathyroidism

HPT is typically sporadic with familial cases accounting for <5% of all cases (Table 20.1).[2] Familial cases of HPT tend to present at a younger age with multigland involvement. There is a higher proclivity for persistent or recurrent disease as compared to sporadic cases, mandating long-term surveillance.

Table 20.1 Familial Causes of Hyperparathyroidism

Disease	Associated Abnormalities	Characteristics
Multiple endocrine neoplasia type 1 (MEN1)	Anterior pituitary tumors Pancreatic neoplasms Parathyroid hyperplasia	Increased rate of persistent and recurrent disease as compared to sporadic disease
Multiple endocrine neoplasia type 2 (MEN2A)	Medullary thyroid carcinoma Pheochromocytoma Parathyroid hyperplasia	Less aggressive than MEN1 disease Screening for RET protooncogene should be performed Screen for pheochromocytoma prior to surgery
Familial isolated hyperparathyroidism	—	Presents at a young age More aggressive than sporadic or MEN-associated disease
Hyperparathyroidism–jaw tumor syndrome (HPT-JT)	Fibroosseous tumors of the mandible Wilms tumor Recurrent parathyroid adenomas	Possible association with parathyroid carcinoma
Familial neonatal hyperparathyroidism	—	Presents with hypotonia and failure to thrive Urgent treatment indicated
Benign familial hypocalciuric hypercalcemia (BFHH)	—	Nonsurgical disease

MULTIPLE ENDOCRINE NEOPLASIA

Multiple Endocrine Neoplasia Type 1

Multiple endocrine neoplasia type 1 (MEN1 or Wermer syndrome) is an autosomal dominant entity characterized by anterior pituitary tumors, parathyroid hyperplasia, and pancreatic neoplasms. Carcinoid tumors of the gastrointestinal tract, bronchus, and thymus as well as ovarian, thyroid, and adrenal tumors have also been reported. Subcutaneous lipomas and angiofibromas are seen in up to one-third of patients. MEN1 is rare but has a penetrance as high as 95% by the age of 40; disease manifestations are thought not to present before the age of 5.[57,58] Patients with MEN1 are found to have a mutation of the *MEN1* tumor suppressor gene at the 11q13 loci that encodes the protein menin.[59]

The most common manifestation of MEN1 is primary HPT, which is present in over 95% of patients under 30 years of age. Diffuse four-gland parathyroid hyperplasia is usually found.[2] MEN1 should be considered in patients who manifest symptoms of pituitary or pancreatic tumors or who reveal a family history of MEN or other endocrinopathies.

Treatment of HPT secondary to MEN1 is a total parathyroidectomy with autotransplantation or subtotal parathyroidectomy. The extent of resection is a subject of debate given a higher rate of persistent or recurrent disease as

compared to patients with sporadic disease after the same operation. Continued exposure of a parathyroid remnant to a yet unknown trophic factor has been postulated to account for the higher rate of persistent or recurrent disease as compared to sporadic hyperplasia cases.[2,60] Persistent disease has often been found to be due to a missed supernumerary gland; thus, bilateral transcervical thymectomy is also advocated.[2,60]

Multiple Endocrine Neoplasia Type 2A

Multiple endocrine neoplasia type 2 (MEN2A or Sipple syndrome) is an autosomal dominant syndrome with high penetrance, characterized by medullary thyroid carcinoma, pheochromocytoma, and HPT. Other disease manifestations include lichen planus, amyloidosis, and Hirschsprung disease. Although the expression may vary, medullary thyroid carcinoma is seen in almost all cases. HPT usually presents after the age of 30 and appears to show a lesser degree of hypercalcemia and symptomatology than that seen in MEN1 or sporadic HPT.[2]

Mutations of the *RET* protooncogene on chromosome 10 that encodes a tyrosine kinase receptor protein have been found to be responsible for this syndrome.[61] Patients with medullary thyroid carcinoma should be screened for the *RET* protooncogene as should their family members if a *RET* mutation is identified.

Prior to surgical treatment, screening for pheochromocytoma with serum and urine catecholamine and metanephrine levels is indicated to avoid intraoperative hypertensive crises and potential disastrous consequences.

Patients with MEN2A have less frequent multiple parathyroid gland involvement and a lower rate of persistent or recurrent HPT after surgery as compared to patients with MEN1, though the rate of recalcitrant disease is still higher than in sporadic cases. During surgery, all four glands are identified with excision of only morphologically abnormal or enlarged glands; thymectomy is usually not indicated as supernumerary glands are rare but should be considered if all four glands are found to be hyperplastic.[2]

FAMILIAL ISOLATED HYPERPARATHYROIDISM

Familial HPT is suspected in hyperparathyroid patients who have a first-degree relative with surgically proven HPT in the absence of a family history of MEN syndromes. Familial HPT patients tend to present younger, between the ages of 10 and 30, with a more aggressive course than sporadic or MEN-associated HPT. Hypercalcemic crisis may even be the presenting picture. Nephrolithiasis is also seen in one-third to one-half of patients. The rate of recalcitrant disease after surgery has been reported to be as high as 33% due to a high incidence of multigland and supernumerary gland disease. Before treatment, all other familial causes of HPT should be excluded.[2]

Hyperparathyroidism–Jaw Tumor Syndrome

Hyperparathyroidism–jaw tumor syndrome (HPT-JT) presents as recurrent parathyroid adenomas, fibroosseous tumors of the mandible and Wilms tumors. Renal cysts and hamartomas can also occur. Primary HPT is the most common manifestation, and a possible association with parathyroid carcinoma has also been reported.[30]

Familial Neonatal Hyperparathyroidism

This is a rare entity with clinical signs manifested as early as the first week of life but occasionally not evident until 3 months or later. Severe hypercalcemia is seen in association with severe hypotonia, failure to thrive, and respiratory distress.[62] Many individuals with familial neonatal HPT have a family history of benign familial hypocalciuric hypercalcemia (BFHH). Familial neonatal HPT is caused by two mutated alleles at the 3q locus; in fact, patients with BFHH have been found to be heterozygous for the mutation. This condition usually requires urgent treatment with a total parathyroidectomy with autotransplantation and bilateral transcervical thymectomy and is associated with a high recurrence rate.[2]

Benign Familial Hypocalciuric Hypercalcemia

BFHH presents the biochemical profile of primary HPT but is a nonsurgical entity. BFHH is inherited in an autosomal dominant fashion and is linked to inactivating mutations of calcium-sensing receptors of the parathyroid cell. A low 24-hour urinary calcium excretion level relative to the degree of hypercalcemia is seen as well as a urinary calcium to creatinine clearance

ratio of <0.01.[2] BFHH usually does not yield any long-term adverse effects and surgery is not indicated.

Clinical Presentation

Symptoms of HPT may be varied and vague. Fatigue, depression, memory problems, malaise, appetite change, abdominal discomfort, constipation, weight loss, musculoskeletal pain, and muscular weakness may serve as the only indicators of disease. Though some patients may appear "asymptomatic," upon specific questioning, most do endorse symptoms. As previously mentioned, routine serum calcium screenings during routine health screenings have aided in the diagnosis of primary HPT in patients in whom the symptoms may be nonspecific and subtle. Consequently, presentation with the "classic" symptoms of hypercalcemia such as osteitis fibrosis cystica, nephrolithiasis, pathologic fractures, and hypercalcemic crisis is presently less common.

In the past, over 50% of patients with HPT suffered nephrolithiasis, mostly composed of calcium oxalate stones, and nephrocalcinosis, compared with ~10% to 20% of patients in recent years.[2,63] Osteitis fibrosis cystica is a condition in which areas of osteoclastic resorption are replaced by peritrabecular fibrosis causing a cyst-like brown tumor. These are most often seen in the phalanges, facial bones, and ribs and generally regress after treatment of the HPT. Previously a common manifestation, currently, it is encountered only in ~2% of patients with HPT.[64] Other effects of PTH on the skeletal system include osteomalacia, osteoporosis, and pathologic fractures. Weakness and fatigue of proximal muscle groups are also seen in ~40% of patients with mild primary HPT, and evidence of EMG changes and atrophy of skeletal muscle seen on biopsy have been reported. Severe disease may even preclude ambulation and function. Most symptoms are noted to improve after parathyroidectomy. Neuropsychiatric symptoms of anxiety, depression, cognitive dysfunction, memory loss, and even frank psychosis are more common in the elderly who have baseline mild cognitive abnormalities. Increased gastrin and gastric acid production secondary to hypercalcemia may also lead to peptic ulcer disease, pancreatitis, and cholelithiasis.[2] Hypercalcemic crisis may occur in cases of significantly elevated calcium levels, causing mental status changes, dysrhythmias, coma, or death.[2]

Long-term investigations of untreated mild HPT have noted that many patients have a benign disease course without significant signs of progression. A significant percentage, however, did show disease progression as evidenced by loss of bone mineral density loss or renal function impairment. There are no known predictive factors to identify which patients will experience a progressive disease course, though younger patients do seem to be at increased risk.[2]

EVALUATION OF HYPERPARATHYROIDISM

History and Physical

A comprehensive history should be performed and should include specific inquiry regarding hypercalcemic symptoms and associated morbidities such as nephrolithiasis or fracture history. A history of current medications is also important to obtain as certain agents such as lithium and thiazide diuretics can induce hypercalcemia. Any history of irradiation is also important to note. A family history of endocrine disorders or related entities is imperative for correct diagnosis, consideration of genetic testing, and evaluation for related entities such as pheochromocytomas, which could have significant ramifications on the treatment plan.

As previously mentioned, physical examination is usually unremarkable without neck masses or neuromuscular abnormalities. A palpable mass in the neck or RLN palsy on laryngeal examination should heighten the suspicion for malignancy.

Laboratory Testing

Serum calcium, intact PTH, albumin, vitamin D, phosphate, magnesium, and chloride levels should be obtained. Forty-three percent of circulating serum calcium is in the free ionized form, which is the major influence on PTH production. Total calcium levels can be affected by disturbances in albumin levels; ionized calcium levels can be affected by acidosis, which decreases calcium binding to albumin and alkalosis, which increases calcium binding to albumin. Parathyroid carcinoma should be suspected if calcium levels are

>14 mg/dL.[2]

In primary HPT, serum total and ionized calcium and PTH levels are elevated. These levels may also be within the normal range but with the PTH level inappropriately high for the associated level of calcium. Low vitamin D levels, however, could signify a secondary HPT. In primary HPT, chloride levels are elevated, whereas phosphate levels are low normal to low with a chloride-to-phosphate ratio >33. If elevated phosphate levels are found in conjunction with elevated calcium levels, causes for intestinal hyperabsorption or hypervitaminosis D should be explored. Renal function should be assessed for a secondary cause of HPT. Alkaline phosphatase levels are also useful to evaluate for active bone disease. A 24-hour urine calcium and creatinine level should be obtained to exclude BFHH. A low urine calcium to creatinine clearance ratio of <0.01 confirms the diagnosis of BFHH.[2]

Malignancy is the second most common etiology of hypercalcemia due to tumor secretion of PTH-related protein. Current PTH assays prevent the cross-reactivity between intact PTH and PHT-related protein. In cases of hypercalcemia from PTH-related protein, intact PTH levels are often suppressed.

Bone densitometry can reveal the catabolic effects of PTH on bone. The distal third of the radius, lumbar spine, hip, and femoral bones are informative sites for measurement. T-scores of ≤−2.5 are an indication for surgical treatment.[65]

There is no role for fine needle aspiration in the diagnosis of parathyroid disorders given the limitations of cytopathologic interpretation and technical difficulty.[5]

LOCALIZATION STUDIES

Localization studies can be extremely helpful in both the primary and reoperative settings. Development of new techniques and advancements of existing methods have improved the accuracy of these tests. This has allowed more directed and limited dissections while attaining similar outcomes as conventional comprehensive four-gland parathyroid explorations.

Ultrasonography

Ultrasound is considered a first-line modality for parathyroid evaluation and localization. Ultrasonography is rapid, relatively inexpensive, easily accessible, and well tolerated and does not expose the patient to any radiation risk. Additionally, it is a noninvasive method, requiring no injection of dye or radiotracer, and thus may be repeated multiple times if needed.[2,5] A 7.5-MHz transducer may provide the best balance between resolution and penetration for evaluation of the parathyroid glands.[66] It is, however, an operator and equipment-dependent modality; consequently, its sensitivity can be influenced by the operator's experience, resolution of the images, and frequency of the transducer.[67]

On ultrasound imaging, normal parathyroid glands are rarely visible. Parathyroid adenomas, hyperplastic glands, and enlarged glands appear as hypoechoic lesions (Fig. 20.2).[66] Parathyroid adenomas appear as homogenous, well-demarcated masses that are of a lower echogenicity than the surrounding thyroid tissue. They are usually oval or bean shaped but may be multilobulated. Occasionally, they may also contain cystic elements.[2,5] Parathyroid carcinomas may have a less sharply defined border but no other specific ultrasound characteristics.[66]

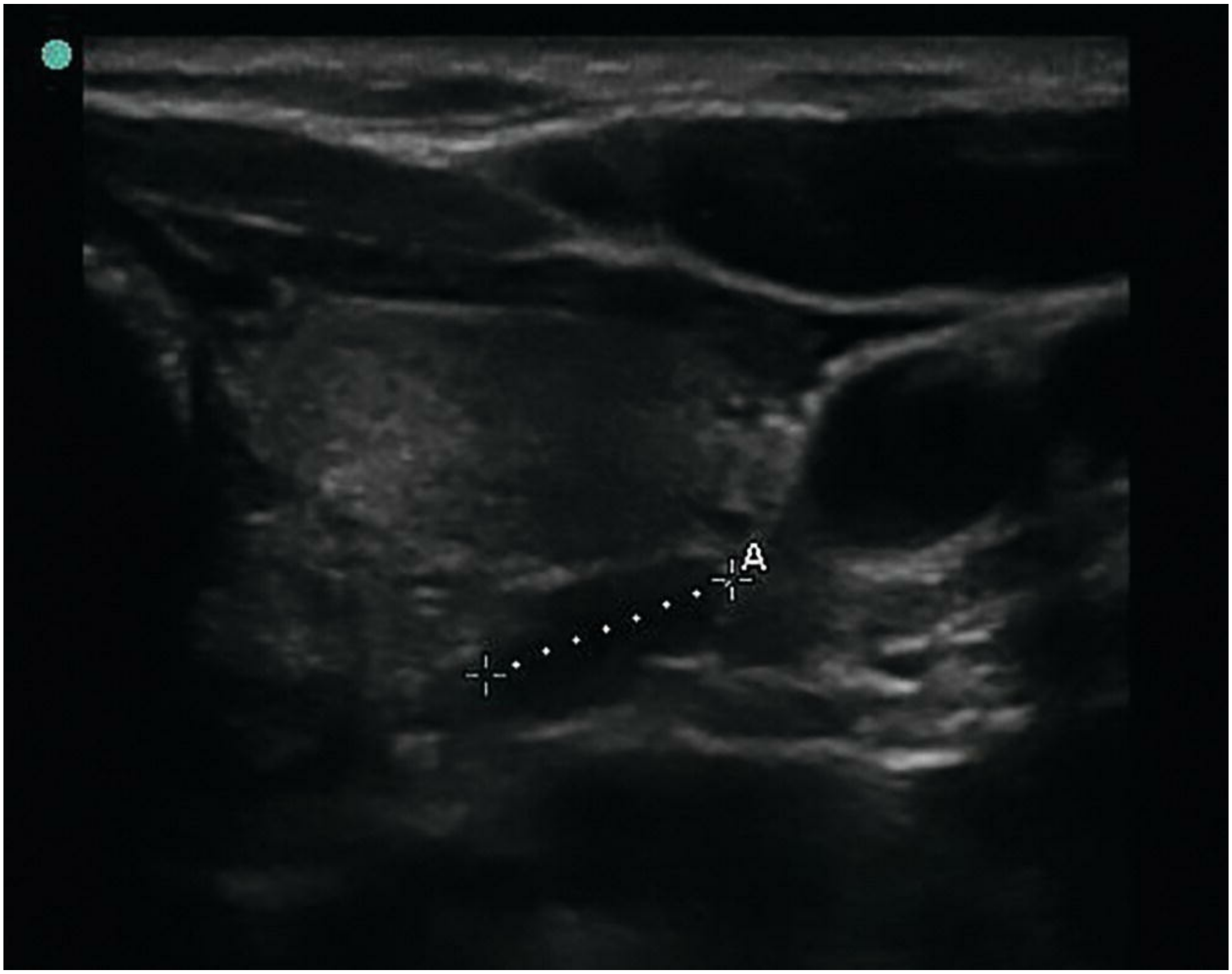


Figure 20.2. Ultrasound image of a hypoechoic lesion corresponding to a parathyroid adenoma (*A*).

Parathyroid glands may be difficult to discern from lymph nodes in a patient with thyroiditis or associated central neck lymphadenopathy. On Doppler imaging, adenomas generally have a distinct vascular pedicle entering at the pole and a characteristic arc or rim of vascularity that represents branching of the feeding artery prior to penetrating into the gland. Conversely, lymph nodes are seen to have an echogenic fatty hilum with a central hilar vessel. Both the transverse and longitudinal planes are useful in identifying parathyroid adenomas. The longitudinal view is particularly helpful in defining position relative to the thyroid gland and vascular structures.[2]

Concurrent nodular thyroid disease, particularly posterior nodules, can significantly limit the evaluation of parathyroid adenomas due to anatomical

distortion of and difficulty discerning nodules from parathyroid glands. Ultrasonography may still be able to discern a thyroid nodule from parathyroid gland that may not be as obvious when viewed by another modality. It may also aid in assessing for intrathyroidal parathyroid adenomas in the setting of cystic thyroid lesions.[68] Additionally, Doppler flow of a discrete blood supply to an intrathyroidal mass may signify an intrathyroidal parathyroid adenoma.[2]

The reported sensitivity and specificity of ultrasonography for the detection of eutopic parathyroid adenomas are ~88% and 98%, respectively, but vary by report. A high positive predictive value has also been described.[69] Surgeon-performed ultrasounds have been promoted by some to be superior to other imaging methods in localizing the correct quadrant of an adenoma and have been advocated as the only preoperative localizing modality necessary.[70–72]

The detection of ectopic parathyroid glands is one limitation of ultrasonography. Mediastinal glands may be difficult to identify due to interference from the sternum, and those in the tracheoesophageal region may be obscured by shadowing and artifact from the laryngeal cartilages.[5] Similarly, retroesophageal and retrotracheal glands are difficult to detect via ultrasound. Deglutition maneuvers during ultrasound may help reveal parathyroid adenomas posterior to the thyroid gland or deep to the clavicles.[66] False-positive results, estimated to be as high as 15% to 20%, may be secondary to the presence of lymphadenopathy, esophageal lesions, or surgical clips.[2,67] Furthermore, in cases of recurrent HPT, ultrasound sensitivity may be lowered due to scar tissue and the probability of an ectopic gland.[66]

Technetium–Thallium Subtraction Scan

Technetium–thallium subtraction scans were one of the earlier applications of nuclear medicine techniques for parathyroid localization. It uses the properties of thallium-201 uptake by both the thyroid and parathyroid glands and Tc-99m uptake by the thyroid gland. Image subtraction of the Tc scan from the thallium scan allows visualization of the parathyroid glands.

The sensitivity of the test has been reported ranging from 78% to 92% and can be significantly lower in previously operated patients.[73,74] The test

may be useful in detecting ectopic glands; however, thallium tends to concentrate in hypercellular areas such as thyroid nodules and can obscure nearby parathyroid glands. Although the thallium–technetium subtraction scan is relatively low risk, it requires prolonged patient immobilization and harbors a high false-positive rate, influenced by motion artifact and concomitant thyroid disease. Given these drawbacks, other methods are generally preferred.[2]

Technetium-99m Sestamibi Scan

Tc-99m sestamibi scintigraphy, initially used for cardiac studies, has been applied to parathyroid imaging. This method relies on the high mitochondrial content of neoplastic parathyroid tissue to sequester and retain more sestamibi than thyroid tissue. A dual-phase scan was developed to produce a planar image to identify areas of increased uptake corresponding to parathyroid adenomas or hyperplasia. The patient is injected with between 20 and 25 mCi of Tc-99m sestamibi, and images are obtained “immediately” at ~10 to 15 minutes and again after an interval of 2 to 4 hours. By the time of the late phase scan, the thyroid tissue will have cleared more sestamibi than the neoplastic parathyroid tissue (Fig. 20.3). These areas of increased uptake likely correspond to parathyroid tissue. Studies have shown the optimum late phase image is obtained at 2 hours.[2]

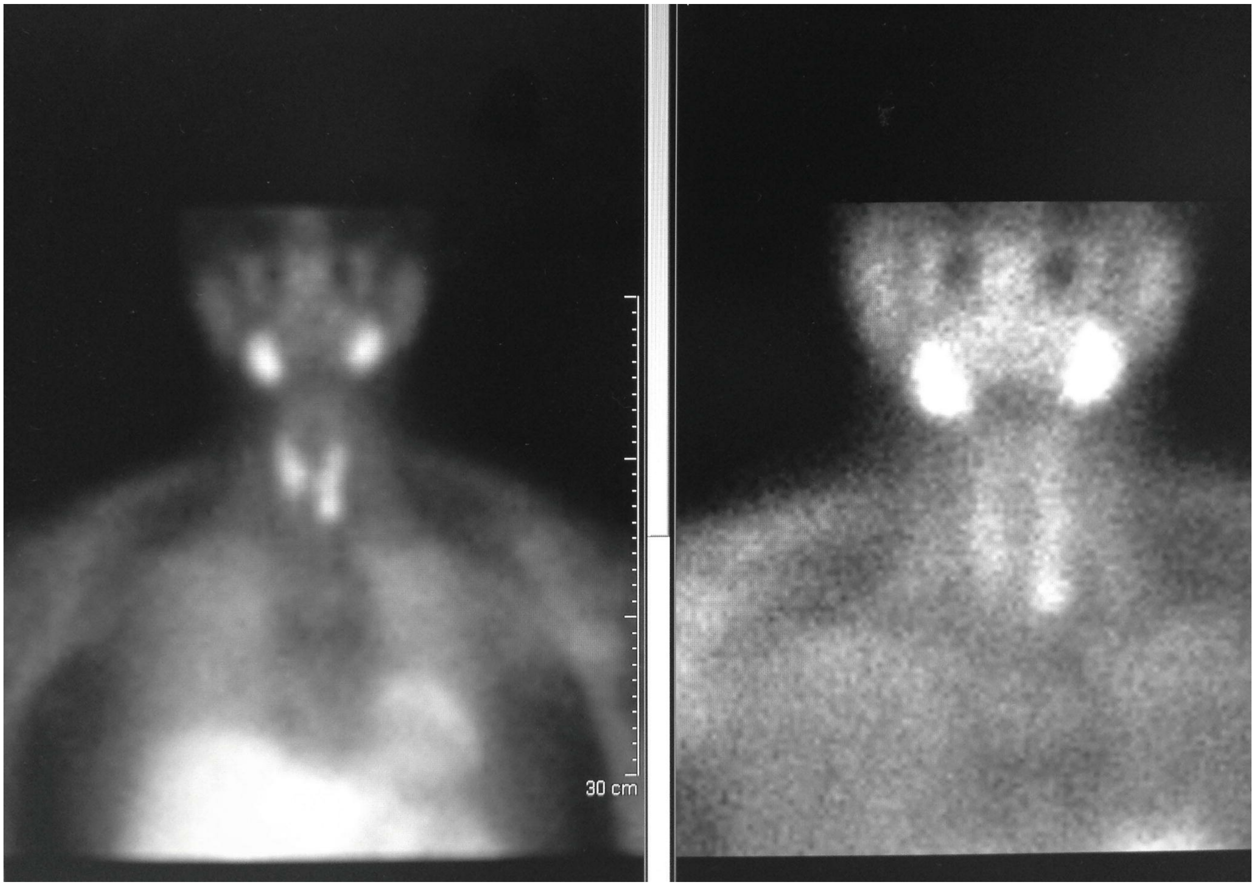


Figure 20.3. Sestamibi scan of a left inferior parathyroid adenoma. The image on the **left** shows the immediate scan. The image on the **right** shows the 2-hour delayed scan.

Sestamibi scanning is superior to ultrasonography in the detection of ectopic glands, particularly mediastinal lesions and double adenomas. False-positives may be seen in the setting of thyroid nodules or Hürthle cell carcinoma lesions. False-negatives may be seen with smaller parathyroid adenomas, inadequate administration of sestamibi, and multigland disease. Parathyroid hyperplasia and presence of Hashimoto thyroiditis may also decrease the accuracy.[2]

Sestamibi scanning has not been widely utilized for cases of secondary and tertiary HPT as some believe it is unnecessary given that a four-gland exploration is generally performed in those instances. However, a high sensitivity and positive predictive value for the detection of ectopic glands has been shown in this population, which may provide better surgical planning and efficiency.[75]

Sestamibi scans have a comparable sensitivity to ultrasonography, and when the two modalities are combined, sensitivity can increase to above 90%. Ultrasound has the advantage of defining the relationship of the gland to the thyroid, and sestamibi scanning has the advantage of detecting ectopic glands. Both are comparably insensitive in situations involving multigland disease.[70,71]

Technetium-99m Sestamibi with Single-Photon Emission Computed Tomography/Computed Tomography

Using a camera collimator that rotates 360 degrees axially around the patient, single-photon emission computed tomography (SPECT) is able to produce a three-dimensional image. This added spatial dimension with the sestamibi–SPECT can better localize ectopic adenomas such as those positioned within the carotid sheath or mediastinum. In particular, the ability to identify anterior and posterior compartment mediastinal lesions helps facilitate surgical planning.

Using specialized software, sestamibi–SPECT may be combined with computed tomography (CT) imaging to enhance the anatomical localization of parathyroid lesions. This single image combines the physiologic information of sestamibi–SPECT with the anatomical information obtained from a CT image. This anatomical refinement can further provide information regarding ectopic glands in thymic, retroesophageal, mediastinal, and intrathyroidal locations. It may also help plan reoperative cases to guide a more focused approach. The localization of parathyroid glands closely associated with the thyroid gland is a significant limitation of this modality.[2] Sestamibi–SPECT/CT has also been shown to be superior to any of these methods alone in detecting multigland disease.[76] According to some reports, combining ultrasound and SPECT/CT for preoperative localization of solitary parathyroid adenomas elevates the sensitivity to as much as 95%.[77]

Computed Tomography

CT imaging is rarely used as a first-line method for parathyroid gland localization. When ultrasound or sestamibi scanning are nonlocalizing or equivocal, CT scanning may provide additional information especially in cases of recurrent or persistent HPT.[78] The information provided is only

anatomic and not physiologic.

CT scanning may be useful in identifying ectopic parathyroid glands in the retrotracheal, retroesophageal, and mediastinal locations, but visualization can be significantly hindered by motion artifact, lymphadenopathy, and nearby vasculature, lending this modality a false-positive rate as high as 50%.[2,5] CT scanning also requires radiation and contrast administration.

Magnetic Resonance Imaging

Magnetic resonance (MR) imaging has a sensitivity ranging from 50% to 80%, for identifying parathyroid adenomas in mediastinal locations in recurrent or persistent cases of HPT.[66,79,80] Parathyroid adenomas have a low signal intensity on T1-weighted imaging and a high intensity on T2-weighted imaging. MR has a high false-positive rate due to difficulty distinguishing lymphadenopathy and thyroid nodules from adenomas.[2] MR imaging does not require the contrast administration or radiation exposure that is needed for CT scanning.

CT and MR imaging have a very limited role in the preoperative localization of parathyroid lesions in the setting of primary surgery due to their relatively high cost and low sensitivity compared to other modalities, but they may have an application in reoperative cases.

4-D Computed Tomography

4-D CT scanning exploits the imaging characteristics of contrast perfusion over time to add functional information. Hyperfunctioning parathyroid glands tend to have a more rapid uptake and washout as compared to normal glands. The sensitivity of 4-D CT has been estimated to be 88% in lateralizing an adenoma and 70% in identifying a specific quadrant.[81] One series found that 4-D CT scanning correctly identified unilateral versus bilateral disease in 95.8% of reoperative cases.[82]

Disadvantages of 4-D CT include significant artifact from involuntary movements, respirations, and deglutition and reduced image quality in larger patients. Additionally, a significant amount of radiation, 10.7 mSv, is delivered to the patient during the examination. This is compared to 7.8 mSv and 6 mSv delivered during an SPECT and standard cervical CT scan,

respectively.[83]

INVASIVE PREOPERATIVE LOCALIZATION

Invasive preoperative localization techniques are rarely used but may provide useful information in the setting of refractory HPT when noninvasive tests are nonlocalizing or equivocal.

Digital subtraction angiography or conventional angiography can be used to visualize parathyroid adenomas because they tend to be hypervascular. Selective arteriography of bilateral thyrocervical trunks, internal mammary arteries, and common carotid arteries can be performed. Catheterization of the thyrocervical trunks can detect glands closely associated with and within the thyroid gland and those in the superior mediastinum along the tracheoesophageal groove. Examination of the internal mammary arteries can identify ectopic glands in the anterior mediastinum or within the thymus. Catheterization of the common carotid arteries can identify parathymic, juxtathyroid, and undescended glands. Some have even described catheterization of the superior thyroid arteries. Complications of parathyroid arteriography can be disastrous including embolic stroke, arterial dissection, and inadvertent injection of contrast into the spinal cord if the costocervical trunk is injected instead of the thyrocervical trunk. The sensitivity of parathyroid angiography has been reported to be ~60%.[2,84]

Selective venous sampling with testing for PTH levels is another tool that can aid in the localization of a parathyroid adenoma. As the venous drainage of parathyroid glands are variable, an arteriogram can act as a guide with the aim of sampling the thymic and inferior thyroid veins; if these have been previously ligated, the vertebral veins may be targeted. The samples obtained from these sites are compared to one from a peripheral vein; if the PTH level is at least double that of the peripheral vein, it is a good indication of a nearby parathyroid adenoma. Internal jugular vein sampling may also indicate the side of the offending gland. This technique may also be used intraoperatively. The sensitivity of selective venous sampling is between 70% and 80%.[84]

Finally, preoperative ultrasound-guided fine needle aspiration of a suspected parathyroid lesion can help identify a hyperfunctional parathyroid

gland. The PTH level of a needle aspirate is a more useful test than cytologic evaluation.[2]

Surgical Management

The success rate of parathyroid surgery has been reported to be above 95% when performed by an experienced surgeon.[85] Preoperatively, patients should be counseled regarding potential complications including temporary or permanent injury to the RLN, temporary or permanent hypocalcemia, and persistent or recurrent HPT.[2]

Surgical Indications

Surgery is always indicated in patients with symptomatic HPT. According to the 2008 NIH guidelines, surgery is indicated for asymptomatic HPT if one of the following criteria is met: serum calcium level at least 1.0 mg/dL above the upper limit of normal, glomerular filtration rate (GFR) of <60 mL/min, a T-score of <−2.5 on bone densitometry scan or history of a previous fragility fracture, or age <50 years old (Table 20.2). The previous indication of a 24-hour urine calcium level of >400 mg/d is no longer included on this most recent guideline.[65]

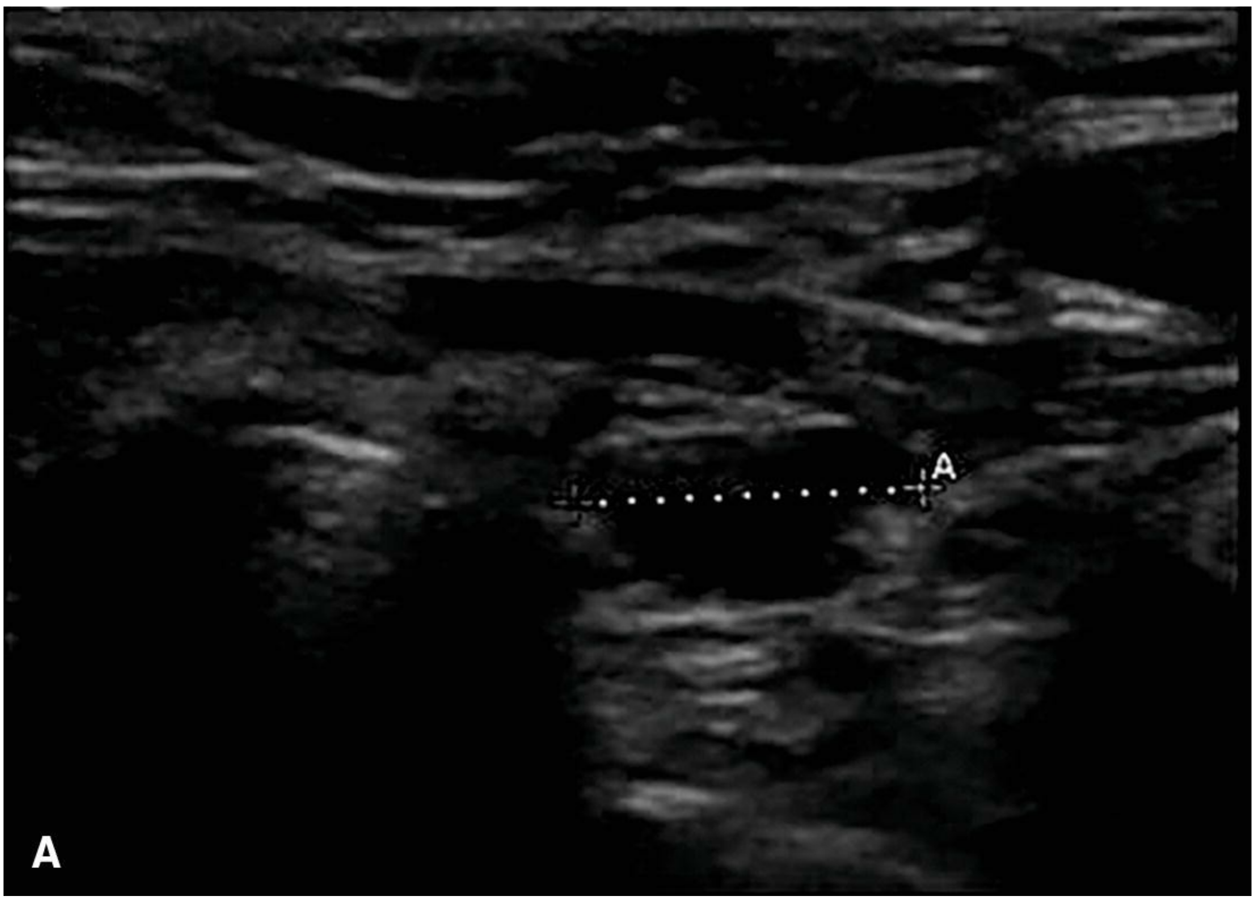
Table 20.2 National Institutes of Health (NIH) Indications for Surgery for Hyperparathyroidism (2008)

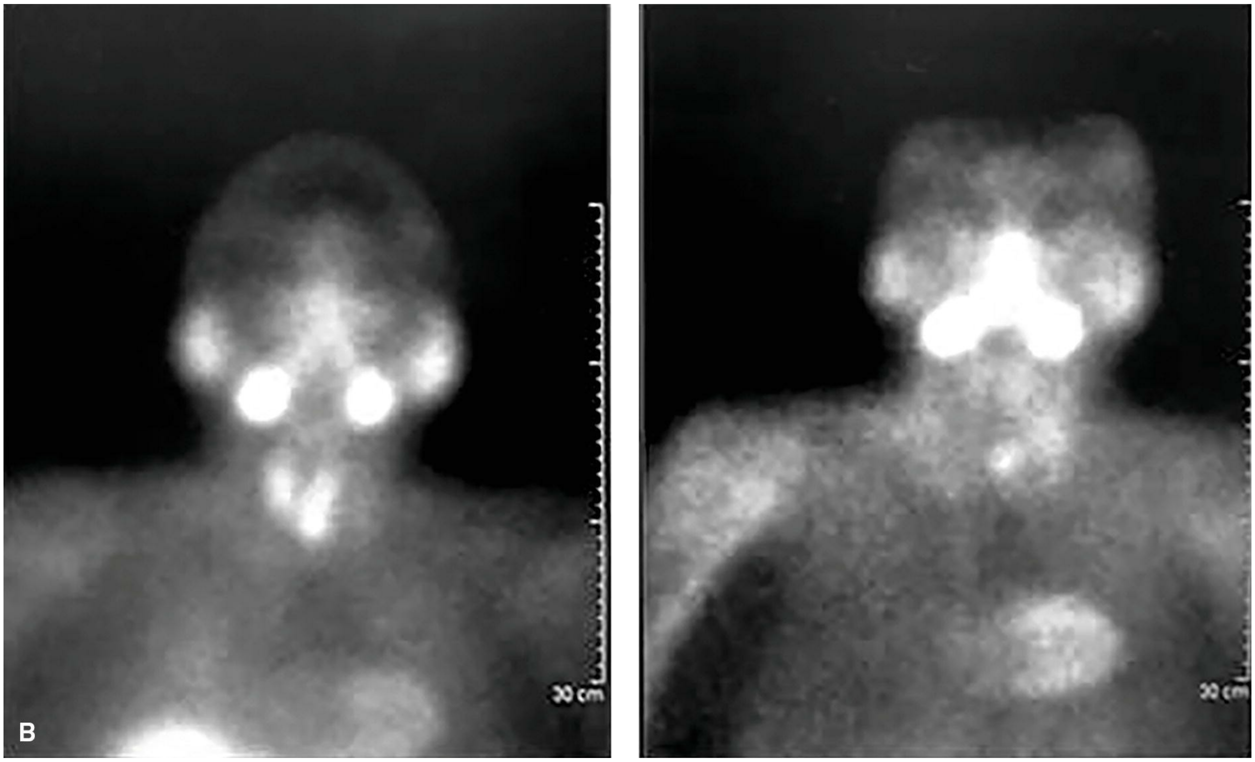
NIH Indications for Surgery for Hyperparathyroidism[57]
Serum calcium level
1.0 mg/dL above the upper limit of normal
Renal function
Glomerular filtration rate (GFR) <60 mL/min
Bone density
T-score <–2.5
History of fragility fracture
Age
<50 years

As previously discussed, there is no indicator to predict which patients with HPT will progress and which will remain asymptomatic. Consideration for surgery is made with the intent to correct any present sequelae and to prevent future consequences.

Intraoperative Parathyroid Hormone Assessment

With the use of preoperative localization studies, the success of minimally invasive surgeries for primary HPT is as high as 95%. The use of an intraoperative PTH assay can further improve that success rate. PTH has a half-life of ~3 to 5 minutes; thus, levels obtained during surgery can quickly provide confirmation that all hyperfunctioning parathyroid tissue has been removed (Fig. 20.4).[85,86]

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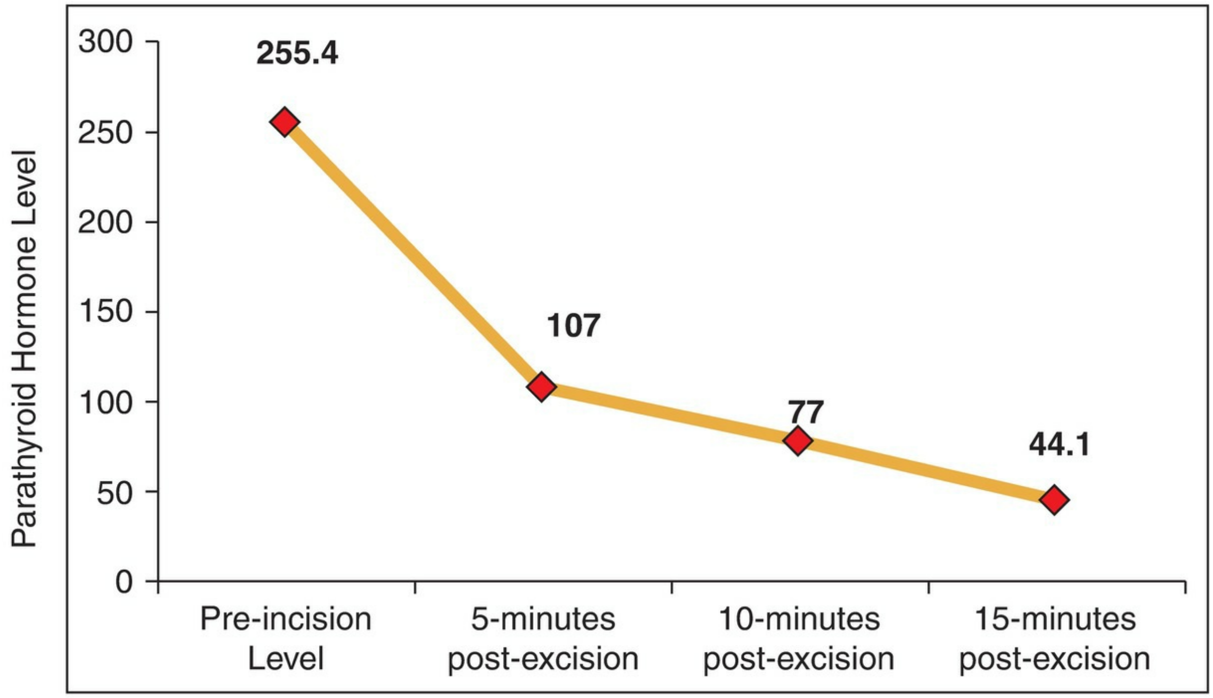

Figure 20.4. A: Ultrasound image of a hypoechoic lesion (*A*).Figure 20.4. (Continued) **B:** Sestamibi scan of a left inferior parathyroid adenoma. Image on the left shows the immediate scan. Image on the right shows the 2-hour scan. **C and D:** Gross appearance of an excised left inferior parathyroid adenoma. **E:** Changes in the intraoperative PTH levels after excision of the parathyroid adenoma.

Intraoperative parathyroid hormone (IOPTH) assays were first reported by Nussbaum in 1988, and their use has become widespread in the United States. They are useful in determining adequate removal of hyperfunctioning parathyroid tissue and in predicting surgical cure, acting like a biochemical frozen section. This real-time assessment of the completeness of surgery can reduce operating time and permit minimally invasive surgery with directed gland dissection. It may also decrease the need for re-exploration in cases of unanticipated multigland disease.[86]

An immunochemiluminescent assay of a peripheral blood sample is used for point-of-care determination of PTH levels with a processing time as rapid as 8 minutes. This speed is conducive to intraoperative assessment and has been shown to be significantly quicker than the turnaround time for central laboratory results.[87] Paired analysis of POC IOPTH compared with central laboratory PTH results revealed that the termination of surgery time based on

POC IOPTH resulted in a mean saving of 16.6 ± 4.5 minutes per case. An overall cost savings has also been shown in using POC IOPTH versus central laboratory methods.[87]

Various recommended algorithms for the timing of PTH level acquisition and criteria for termination of the procedure have been proposed.[85,88,89] Based on analysis of data of a single-surgeon experience from our institution, we prefer to obtain a preincision PTH level followed by a 5-minute postexcision level and, if needed, 10- and 15-minute postexcision levels. In this series of 112 patients with primary HPT, 63.5% of cases were able to be concluded after an adequate decrease (a 50% drop from the preincision baseline into the normal laboratory reference range) in the PTH level obtained at five minutes postexcision. Furthermore, there were no false positives of cure based on this 5-minute level.[85]

In cases of multigland disease such as hyperplasia or double adenoma, intraoperative PTH levels can be instrumental in determining the completeness of surgery and minimizing the extent of surgery. An initial drop may give way to a plateau of the PTH level, signifying that more hyperfunctional parathyroid tissue is present. The PTH levels will further drop with the subsequent excision of this retained hyperfunctional parathyroid tissue.[5] Evidence also suggests that patients with HPT who have low preincision PTH levels may not have as predictable a decrease in PTH levels as patients with higher levels. Such patients may also be at risk for unrecognized multigland disease.[90]

Intraoperative Fine Needle Aspiration

Although not used routinely, point-of-care intraoperative PTH assay of needle aspirates is an accurate method to differentiate parathyroid from nonparathyroid tissue when the distinction is not clear. The mean PTH levels of parathyroid tissue needle aspirates have been shown to be 3,338.9 ± 714 pg/dL as compared to 8.7 ± 1.5 pg/mL for nonparathyroid tissue aspirates. When compared to frozen section analysis, it is less expensive per test and yields more rapid results, affording the potential to shorten operative time.[51]

SURGICAL PRINCIPLES

Parathyroid surgery has traditionally consisted of a bilateral, four-gland exploration. With the development of preoperative localization studies and intraoperative PTH level assessment, a more focused dissection can be performed in appropriate cases. Each case should still be approached with the potential that a four-gland exploration and possibly a superior mediastinal dissection may be required, and patients should be counseled as such.[91]

A thorough knowledge of the embryology and anatomy of the parathyroid glands is paramount in parathyroid surgery. A systematic and meticulous dissection should be undertaken with attention to strict hemostasis as staining of the tissues can obscure identification of parathyroid glands. There should be a low threshold for identification of the RLN not only to ensure nerve integrity but also to aid in distinguishing inferior from superior parathyroid glands. Gentle palpation may also help to identify a parathyroid adenoma, particularly those lying along the prevertebral fascia.[5]

Normal-appearing parathyroid glands and their respective blood supplies should be preserved. In ambiguous cases, such as multigland disease, a biopsy may be performed with care to remove only tissue from the distal tip of the gland in order to not disrupt the blood supply. If the viability of a normal parathyroid gland is questioned, reimplantation should be considered.

Dissection should commence on the side intimated by the preoperative localization studies. The thyroid gland is mobilized to expose the eutopic sites of the parathyroid glands. The middle thyroid vein may be ligated if needed to improve exposure; division of the superior and inferior pedicles is usually not necessary.[5] A systemic approach to identifying parathyroid glands is necessary to prevent overlooking abnormal glands.

In cases of primary HPT where both sestamibi and ultrasound are nonlocalizing, which occurs in 10% of cases, a four-gland exploration may be planned. In such cases, a sestamibi–SPECT/CT may provide important information as it is more sensitive and specific for localizing ectopic glands.[91]

In a four-gland exploration, a unilateral dissection is first performed, followed by exploration of the contralateral neck if a suspicious gland is not identified. If an inferior gland is not found, anterior mediastinal dissection is performed. It may be easier to examine intrathymic contents ex vivo after an anterior superior mediastinal dissection rather than in vivo unless an adenoma

is obvious. If an inferior gland is still elusive, systemic investigation of the retroesophageal area and carotid sheath follow. Unless a suspicious lesion is noted on ultrasound, a thyroid lobectomy is not performed. Four-gland explorations with superior mediastinal dissection yield higher rates of injury to the RLN due to its identification and longer length of dissection compared to more limited dissections. Additionally, in tracing along the RLN, normal parathyroid glands are at risk for becoming devascularized. As a result, higher rates of permanent hypocalcemia occur as compared to limited dissections. Thus, if the blood supply to a normal gland appears to be compromised, it should be autotransplanted.

If all four glands are located and appear normal, a supernumerary gland or four-gland hyperplasia is considered. A cervical thymectomy is performed if a supernumerary gland is suspected. If hyperplasia is suspected, biopsies of the identified glands are sent for frozen section analysis to assess for hypercellularity.

Ectopic parathyroid glands can be found anywhere from the nasopharynx to the inferior pericardium but are most commonly identified in the anterosuperior mediastinum, the majority of which are intrathymic or intimately associated with the thyrothymic ligament.[91]

Transcervical mediastinal dissection usually entails an anterosuperior dissection in conjunction with a thymectomy. This is usually performed when preoperative studies localize to the mediastinum and primary HPT recurs or persists after a four-gland exploration and in cases of MEN1 and secondary HPT, which have higher rates of supernumerary glands. A posterosuperior mediastinal dissection is uncommonly required when search for an ectopic superior gland or supernumerary gland is otherwise unsuccessful.[91]

Most adenomas, including those located in superior mediastinum, are accessible via a transcervical approach with only 2% requiring a thoracic approach.[91] Transcervical access is attempted initially with conversion to a transsternal approach if the lesion is too deep to access through the neck. Sternotomy may occasionally be planned as a solo approach for ectopic glands if indicated on a preoperative localization study.[5,83]

Lesions in certain locations are more likely to require a thoracic approach, including those inferior to the manubrium, brachiocephalic vein, or aortic arch. Techniques such as reverse Trendelenburg positioning, cervical

extension, anterior suspension, sternal or clavicular traction, or posterior displacement of the brachiocephalic vessels may aid dissection as far inferior as the level of the aortic arch through a transcervical approach. Lesions located within the aorticopulmonary window or deep in the mediastinum will undoubtedly require an isolated transthoracic approach. Historically, adenomas in the deep mediastinum were removed through a median sternotomy, but video-assisted thoracoscopic surgery (VATS) has yielded high success rates, particularly for posterior inferior mediastinal lesions, with decreased morbidity and faster recovery.[91]

SURGERY FOR MULTIGLAND DISEASE AND SECONDARY HYPERPARATHYROIDISM

In patients with multigland disease, for instance, those with renal HPT or MEN, all four parathyroid glands identified before any glands are removed. Once all glands are visualized, their size and gross appearances are noted and compared. In cases of renal HPT, patients eligible for renal transplantation should undergo a 3.5 gland parathyroidectomy; patients not eligible for transplantation should undergo a total parathyroidectomy with autotransplantation.[91]

When a subtotal parathyroidectomy is indicated, the smallest and most normal-appearing gland is selected for the remnant. Meticulous dissection of this gland is performed to preserve the blood supply. A medium vascular clip is used to mark the remnant, and the portion of the gland distal to the vascular supply is excised. If the viability of the remnant is dubious, it should be removed and the next most normal-appearing gland selected for the remnant. When the viability of the remnant gland is confirmed, dissection and excision of the remaining glands are then performed (Fig. 20.5). Prior to excision of the last gland, confirmation of the remnant viability is recommended. Care should be taken to prevent any spillage of parathyroid tissue that could lead to recurrent disease.

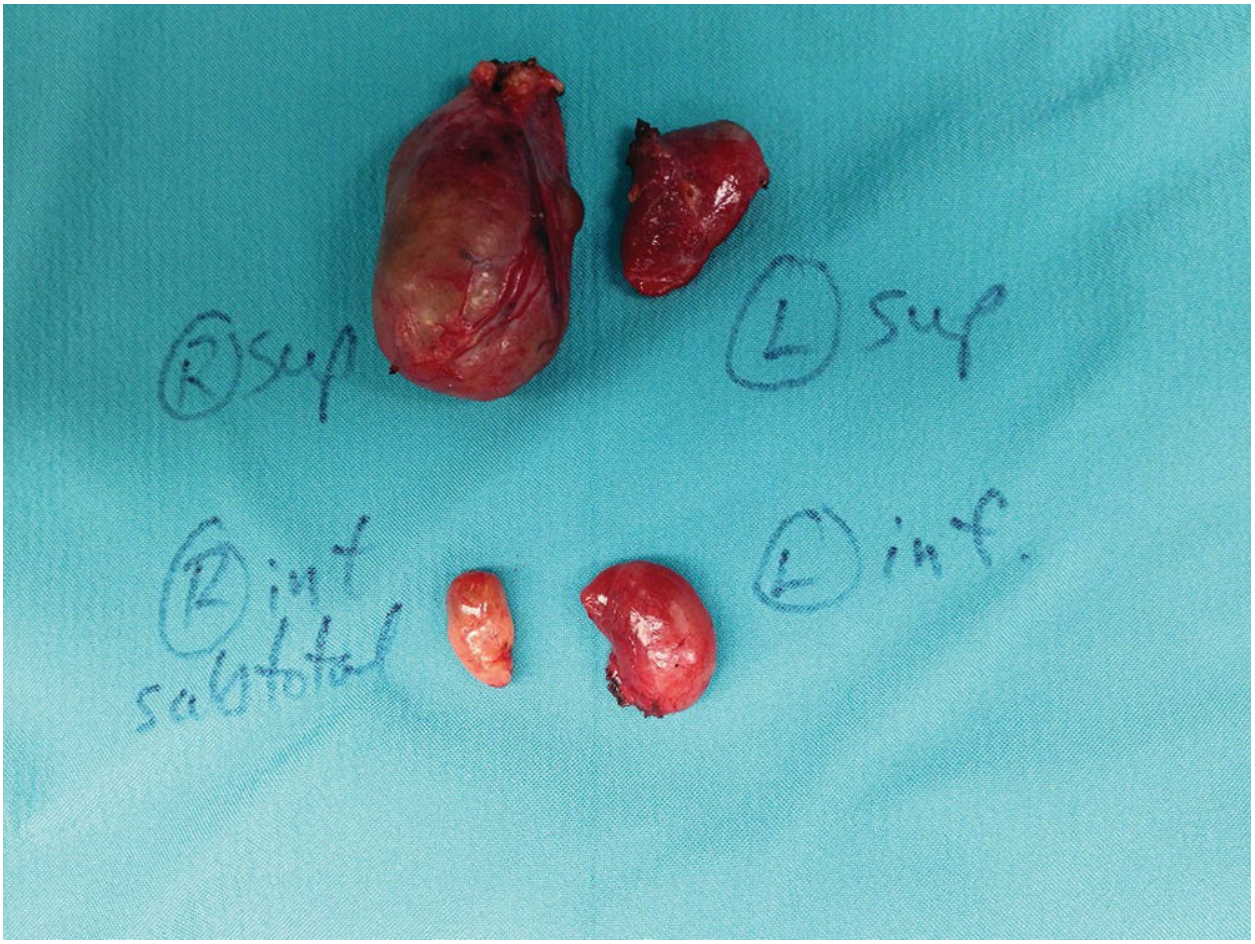

Figure 20.5. Gross specimen of a subtotal parathyroidectomy performed in a patient with secondary HPT from renal disease. Note the asymmetry of the parathyroid glands. The most normal-appearing gland was selected to leave a remnant in vivo.

More aggressive resection with a total parathyroidectomy with or without autotransplantation and bilateral cervical thymectomy is reserved for virulent disease with higher rates of recurrence. This is recommended for cases of familial hyperplasia, neonatal HPT, MEN1, and select cases of secondary HPT.

CAUSES OF SURGICAL FAILURE

The most common finding on re-exploration for persistent HPT is a missed single parathyroid adenoma. One series of 288 reoperations found a solitary adenoma in 77% of the cases, most of which were in eutopic locations.[2]

Twenty-seven percent of adenomas were found in the tracheoesophageal groove. Many were found apposed to the RLN suggesting insufficient dissection around the nerve during the initial operation. Review of previous operative and pathology reports may be informative in regard to remaining glands, missed areas of dissection, and thoroughness of exploration. Greater incidences of temporary or permanent RLN injury and hypocalcemia are seen after reoperations.[2]

MINIMALLY INVASIVE PARATHYROID SURGERY

Recent advances in preoperative localization studies and IOPTH assays have allowed minimally invasive parathyroid surgery with success rates comparable to that of conventional bilateral exploration. This approach may be accomplished with or without endoscopic visualization. In cases of a solitary adenoma with concordant preoperative ultrasound and sestamibi findings, a unilateral quadrant-directed dissection through a small incision with biochemical confirmation of complete removal of hyperfunctioning tissues is certainly feasible. The patient must be counseled and the surgeon prepared for a more comprehensive dissection if IOPTH levels remain elevated.

Minimally invasive parathyroidectomy has the advantages of a shorter operating time, lesser degree of dissection, decreased time of recovery, and less risk of complications (i.e., hypocalcemia) due to minimal dissection. The ability to perform the procedure through an incision as small as 15 to 20 mm also allows improved cosmesis. It has also been shown to be cost-effective when compared to conventional open procedures.

Multiple studies have shown that the long-term biochemical cure rates of minimally invasive parathyroid surgery are comparable to those of conventional parathyroidectomy.[92,93]

Radioguided Parathyroidectomy

Radioguided parathyroidectomy was developed by Norman and Chheda in 1997 to help identify hyperfunctional parathyroid tissue intraoperatively.[94,95] Patients are injected preoperatively with Tc-99 and a handheld gamma

detection probe is used intraoperatively to assess the radioactivity of excised tissue. Adenomatous parathyroid tissue has an increased affinity for the radiotracer due to its abundant amount of mitochondria. Parathyroid tissue that demonstrates at least 20% of the radioactivity of the background surgical field is likely hyperfunctional. Some authors report increased success rates with this technique,[96] whereas other groups have found that that radioactivity levels are not a substitute for changes in intraoperative PTH levels.[97]

POSTOPERATIVE CONSIDERATIONS

Postoperative hypocalcemia may be seen in patients as a result of “bone hunger” from severe skeletal demineralization caused by the hyperparathyroid state. Some may even develop symptoms of hypocalcemia, including tetany, due to the rapid decline in calcium levels even if the serum calcium levels remain in the normal range. Serum calcium levels should reach a nadir at ~48 hours postoperatively. Concomitant hypomagnesemia should be treated as this condition prevents appropriate repletion of calcium levels. In our practice, we prescribe a standard 3-week taper of a combined calcium and vitamin D supplement to prevent postoperative hypocalcemia.

HYPOPARATHYROIDISM

Hypoparathyroidism is most commonly encountered after thyroid or parathyroid surgery. It may also be seen in congenital syndromes such as DiGeorge syndrome in which abnormal development of the third and fourth branchial pouches leads to agenesis of the parathyroid glands.

Symptomatic hypoparathyroidism requires timely treatment with calcium and active vitamin D metabolites. Administration of intravenous calcium may be required in cases of severe hypocalcemia where serum calcium levels are below 7 mg/dL, signs of mental status changes are present, and neuromuscular irritability such as tetany, laryngospasm, or bronchospasm manifests. In cases where calcium correction is too rapid or in patients taking digoxin, arrhythmias can occur.[91]

Magnesium and vitamin D levels should be optimized prior to surgery as suboptimal levels can exacerbate hypocalcemia. Diligent identification of parathyroid glands and preservation of parathyroid blood supply are

instrumental in preventing postoperative hypocalcemia.

CONCLUSION

The understanding and treatment of parathyroid disease have progressed significantly since their initial discovery. Advancements in biochemical screening, preoperative localization, and intraoperative assessment techniques have allowed a high rate of successful surgery and have even permitted minimally invasive procedures to be performed accurately and safely.

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21 Cancer of the Salivary Glands

Yekaterina A. Koshkareva Robert L. Ferris

Cancers of the salivary glands are a distinctive group of neoplasms arising in the major and minor salivary glands. The distinguishing features of these cancers include their low incidence, histopathologic heterogeneity, presentation at multiple anatomic sites, and wide spectrum of clinical behaviors. The goal of this chapter is to provide a contemporary, comprehensive review of the demographics, etiology, pathology, and presentation of cancers of the salivary glands, as well as a summary of current recommendations for staging and treating these cancers.

Surgical Anatomy

There are two types of salivary glands; the major salivary glands, which are readily identifiable, with anatomically distinct excretory ducts, and the minor salivary glands, which are less easily identifiable, smaller, and lack distinct ducts. The parotid, submandibular, and sublingual glands are the major salivary glands, whereas the minor salivary glands are not individually named and are found throughout the length of the upper aerodigestive tract.

Parotid Gland

The paired parotid glands are the largest of the major salivary glands and form the lateral portions of the facial contour. The parotid gland is bounded by the cartilage of the external auditory canal posteriorly, the mandibular ramus and the masseter muscle medially, and the buccinator muscle anteriorly. The superior border is the zygoma, whereas the inferior aspect, also known as the “tail,” lies over the posterior belly of the digastric muscle

medially and sternocleidomastoid (SCM) muscle laterally. The medial portion of the parotid gland abuts and sometimes extends into the parapharyngeal space (Fig. 21.1). Accessory parotid tissue may be found anterior to the body of the gland, along the course of Stensen duct, in 21% of the population.[1] The gland is encased by a capsule derived from the deep cervical fascia and is further enveloped by the superficial musculoaponeurotic system (SMAS) in the face and the platysma in the neck. The parotid (Stensen) duct travels along the surface of the masseter and turns medial at its anterior border, transversing the buccal adipose tissue pad and the buccinator, and opens into the oral cavity opposite the second maxillary molar.

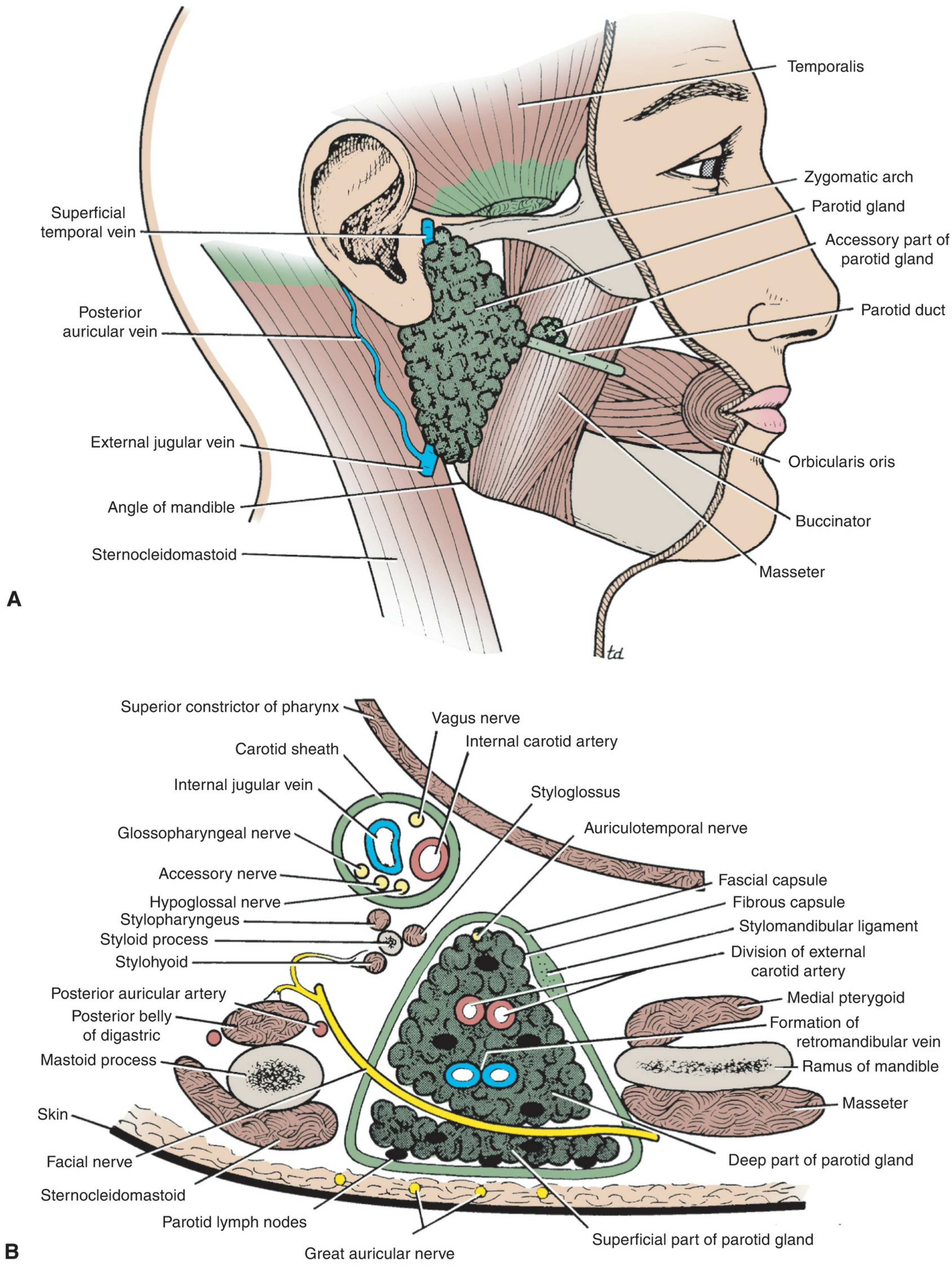


Figure 21.1. A and B: Parotid gland anatomy. (From Snell RS, ed. *Clinical*

Anatomy by Regions. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

The arterial supply of the parotid gland comes from the two terminal branches of the external carotid artery: the superficial temporal and internal maxillary arteries. The venous outflow is collected by the respective superficial temporal and internal maxillary veins, which then join to form the retromandibular vein. The anterior division of the retromandibular vein along with the anterior facial vein forms the common facial vein. The posterior division joins the posterior auricular vein to drain into the external jugular vein.

There are as many as 20 lymph nodes within and adjacent to the capsule of the parotid gland, and these nodes are the first echelon of nodes to receive lymphatic drainage from the soft tissues of the temporal scalp, cheek, ear, and external auditory canal. Hence, the parotid lymph nodes may harbor metastatic foci from cancers that arise from these sites. Efferent parotid lymphatics drain into the lymph nodes of the superior and middle deep jugular chain.

Another important anatomic structure that must be considered in the management of parotid tumors is the facial nerve, which runs through the gland and serves as a landmark that separates the parotid into superficial and deep lobes. The main trunk of the facial nerve exits the stylomastoid foramen and enters the parenchyma of the parotid gland, where it typically divides into an upper and lower division. It then further subdivides into its five principal branches, but the arborization of the nerve can be quite varied.[2] The point at which the main trunk of the facial nerve divides for the first time is referred to as the pes anserinus. The lower division contains the branches to the platysma (cervical branch) and the lower lip depressors (marginal mandibular branch). The marginal mandibular nerve is located deep to the platysma muscle and lateral to the facial vein and the capsule of the submandibular gland. The midface division (zygomaticobuccal branches) supplies innervation to the buccal, zygomatic, and lower eyelid muscle groups. The buccal branch is identified in the vicinity of the parotid (Stensen) salivary duct. The upper face division (frontal branch) travels lateral to the superficial layer of the deep temporal fascia to supply the frontalis and superior orbicularis oculi muscles.

Other nerves of importance encountered during parotid gland surgery are the greater auricular and auriculotemporal nerves. The greater auricular nerve is found on the lateral surface of SCM muscle, along the lateral border of the parotid gland. Its anterior and posterior branches provide sensation to the inferior aspect of the auricle and periauricular skin. The auriculotemporal nerve is a branch of the fifth cranial nerve (trigeminal nerve), which travels along with the superficial temporal vessels, posterior to the parotid, providing sensation to the temporal region. The auriculotemporal nerve also provides parasympathetic innervation to the parotid gland from the otic ganglion. After resection of the parotid salivary tissues, these fibers may form an aberrant innervation with sweat glands leading to perspiration in response to the gustatory stimuli, a phenomenon known as gustatory sweating (Frey syndrome).

Submandibular Gland

The paired submandibular glands are located in the superior aspect of the anterior neck, bounded superiorly and laterally by the body of the mandible. The platysma muscle covers the gland’s lateral border, and the hyoglossus muscle lies medial to the gland. The gland resides posterior to the lateral border of the mylohyoid muscle. The submandibular (Wharton) duct originates from the multiple smaller branches originating from the medial aspect of the gland. It courses anteriorly and superiorly first between the mylohyoid and the hyoglossus muscles and then between the sublingual gland and the genioglossus muscle. The duct is situated between the lingual and hypoglossal nerves while on the surface of the hyoglossus, but at the anterior border of the muscle, the branches of the lingual nerve cross the duct to assume a more medial position. The submandibular duct travels a total distance of ~5 cm and empties into the anterior floor of the mouth.

The facial artery provides the main blood supply to the submandibular gland. This artery courses deep to the posterior belly of the digastric muscle and travels either along the medial aspect of the gland or through the gland parenchyma and traverses the lower border of the mandible at the antegonial notch curving over the insertion of the masseter muscle into the anterior border of the mandible. Venous drainage is supplied by the anterior facial vein.

Although there is no lymphoid tissue within the parenchyma of the

submandibular gland, there are a number of pre- and postvascular lymph nodes adjacent to the facial vessels, which run over the lateral aspect of the gland, which serve as the first echelon nodes for lymphatic drainage from the lip, oral cavity, and skin of the anterior face. These lymphatics can also drain into the deep jugular chain of nodes. Enlargement of the submandibular nodes can be difficult to distinguish from a primary tumor of the submandibular gland, and a metastatic process within these nodes may also invade the adjacent gland by direct extension.

Similar to the parotid, the submandibular gland lies in anatomical proximity to the facial nerve. The marginal mandibular branch runs along the inferior border of the mandible, just deep to the platysma muscle and lateral to the fascia of the gland. Additionally, the lingual and hypoglossal nerves are located deep to the medial surface of the gland, whereas the nerve to the mylohyoid is adjacent to the superior aspect of the gland (Fig. 21.2).

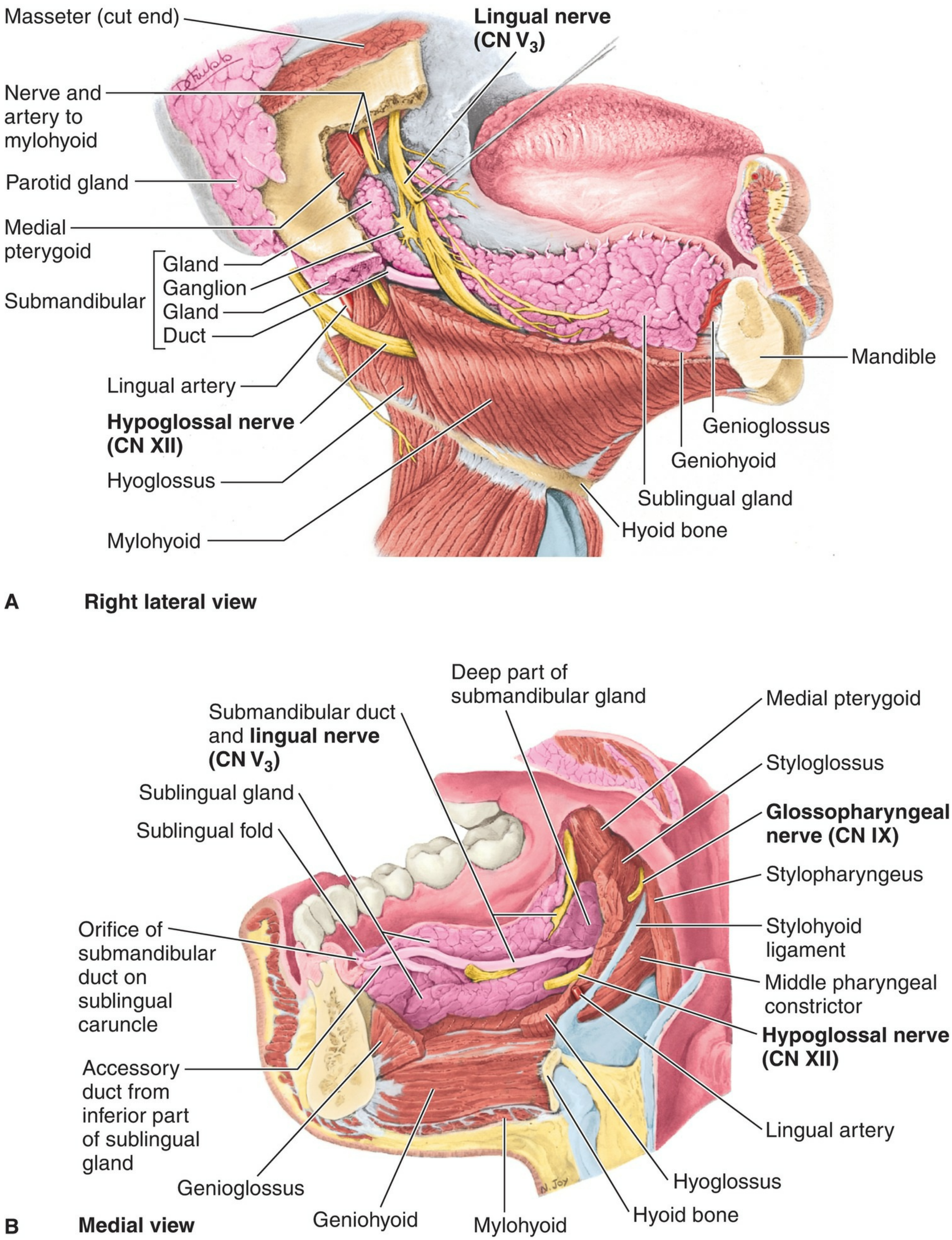


Figure 21.2. A and B: Submandibular gland anatomy. (From Moore KL, Agur AMR, Dalley AF, eds. *Clinically Oriented Anatomy*. 7th ed. Baltimore,

MD: Lippincott Williams & Wilkins; 2013.)

Sublingual Glands

The sublingual glands are also found bilaterally. They are located deep to the mucosa of the floor of the mouth and drain directly into the oral cavity through numerous small ducts. Tumors of the sublingual glands can be difficult to distinguish from those arising within the submucosal minor salivary glands of the floor of the mouth.

Minor Salivary Glands

There are over 600 minor salivary glands distributed throughout the length of the upper aerodigestive tract, and approximately half of them are located on the hard palate. Tumors can arise in these glands in such diverse sites as the oral cavity, oropharynx, larynx, pharynx, nose, nasopharynx, and paranasal sinuses. Additionally, small rests of heterotopic salivary tissue can be located within the cervical lymph nodes, mandible, thyroid gland, and the middle ear.[3]

Anatomic Tumor Classification

Over 75% of salivary gland neoplasms originate in the parotid gland (mainly in the superficial lobe), with submandibular and minor glands comprising the rest. Approximately 80% of parotid gland tumors are benign. The likelihood of a submandibular gland lesion being benign is much less, around 43%. Finally, lesions arising within the minor salivary gland lesions are more likely to be malignant (up to 60%), especially if they originate outside of oral cavity (Fig. 21.3).[4–12]

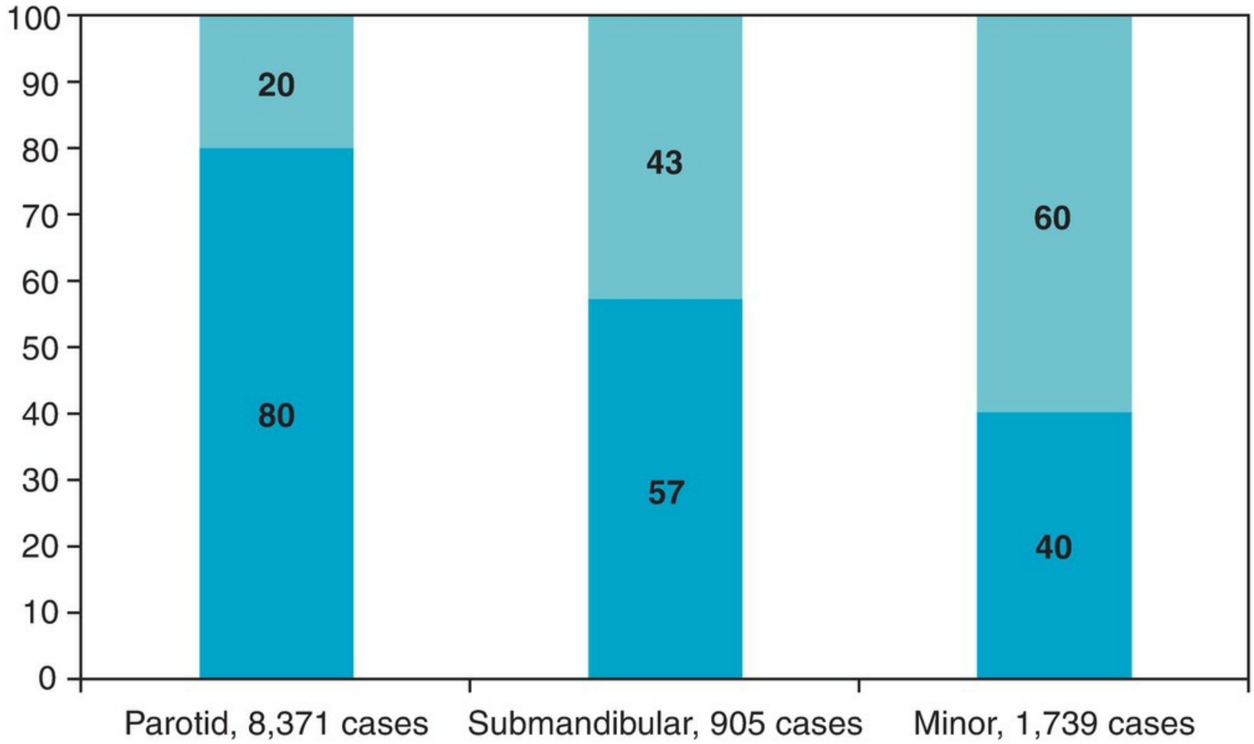


Figure 21.3. Relative ratio of benign versus malignant salivary neoplasms at various anatomic sites. (Dark blue, benign; light blue, malignant.)

Histology and Histogenesis of Salivary Gland Tumors

The salivary glands originate as ingrowths from the oral epithelium, which makes them of ectodermal descent. These ingrowths go on to form the ductal structure. The basic functional unit of a salivary gland is an acinus, made up of serous and mucinous cells. The acini release their secretions into an intercalated duct, which later becomes a larger striated duct, which eventually empties into an excretory duct. The myoepithelial cells surrounding the acini and intercalated ducts are capable of contraction and help with saliva transport (Fig. 21.4). The parotid gland is almost exclusively serous. The submandibular and sublingual glands are both mixed, but the serous component predominates in submandibular glands, whereas the mucinous element is dominant in sublingual glands.[13]

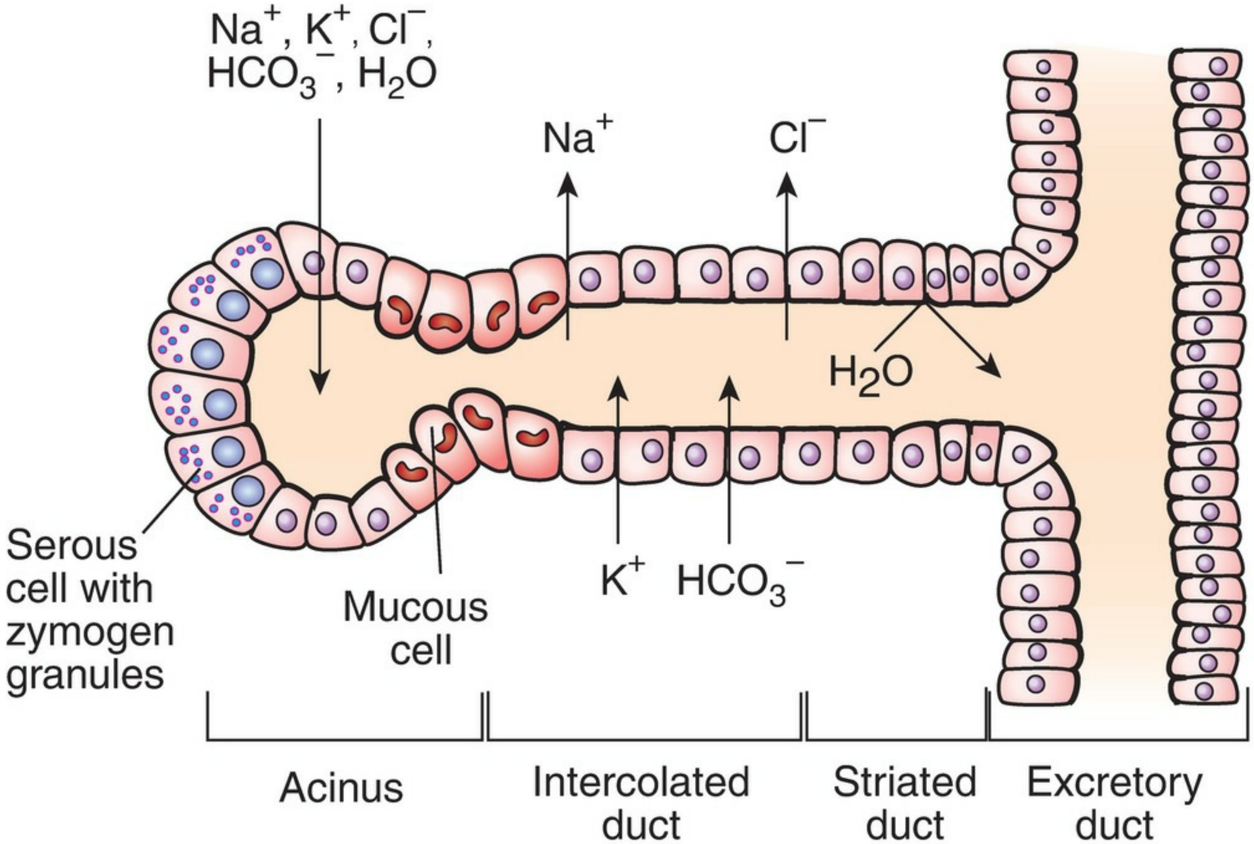


Figure 21.4. Functional unit of a salivary gland. (From Rhoades RA, Bell DR, eds. *Medical Physiology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2012.)

There are two leading theories of the histogenesis of tumors of the salivary glands. According to the multicellular theory, each cancer arises from a particular cell type within the secretory unit.[14] For example, Warthin and oncocytic tumors are thought to arise from striated ductal cells and acinic cell tumors from acinar cells.[15] The bicellular reserve cell theory states that the development of any salivary gland neoplasm can be traced to the basal cells of either the excretory or the intercalated ducts, which are thought to be the reserve cells capable of differentiation. According to this model, pleuripotent intercalated duct basal cells give rise to salivary neoplasms of adenomatoid origin (pleomorphic adenoma, oncocytic tumors, acinic cell and adenoid cystic carcinomas). The epidermoid tumors (squamous cell and mucoepidermoid carcinomas) are then thought to be derived from the excretory duct reserve cells.[16]

Histologic Classification

Salivary gland malignancies remain a diagnostic challenge for pathologists due to the rarity of these tumors as well as the wide histopathologic diversity and heterogeneity of these cancers. The modifications to the original classification scheme described by Foote and Frazell have resulted in the current World Health Organization (WHO) classification.[17] The most recent WHO classification published in 2005 recognizes 13 benign and 24 malignant tumor subtypes, which are summarized in Table 21.1.[18]

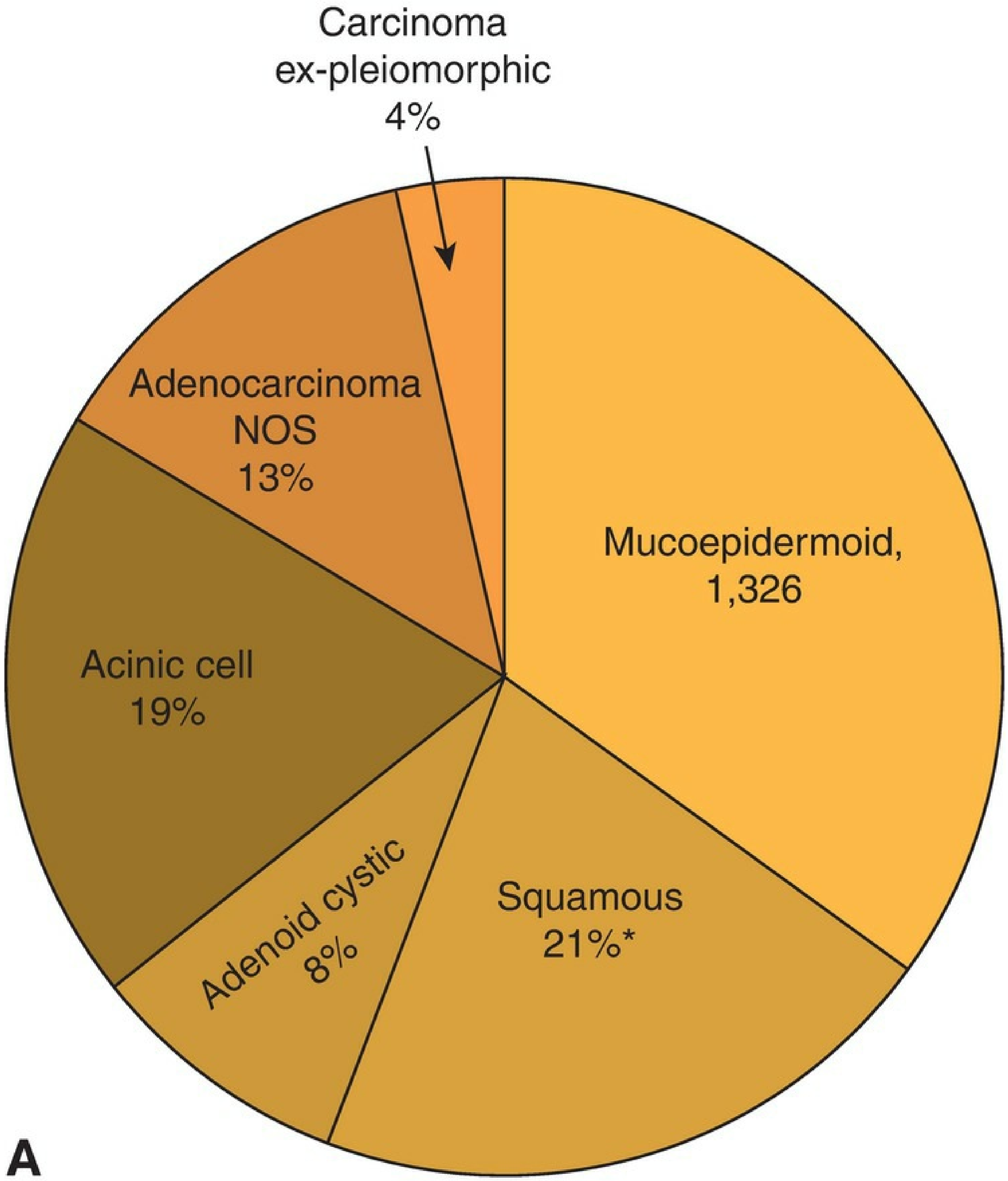
Table 21.1 WHO Histologic Classification of Salivary Gland Neoplasms

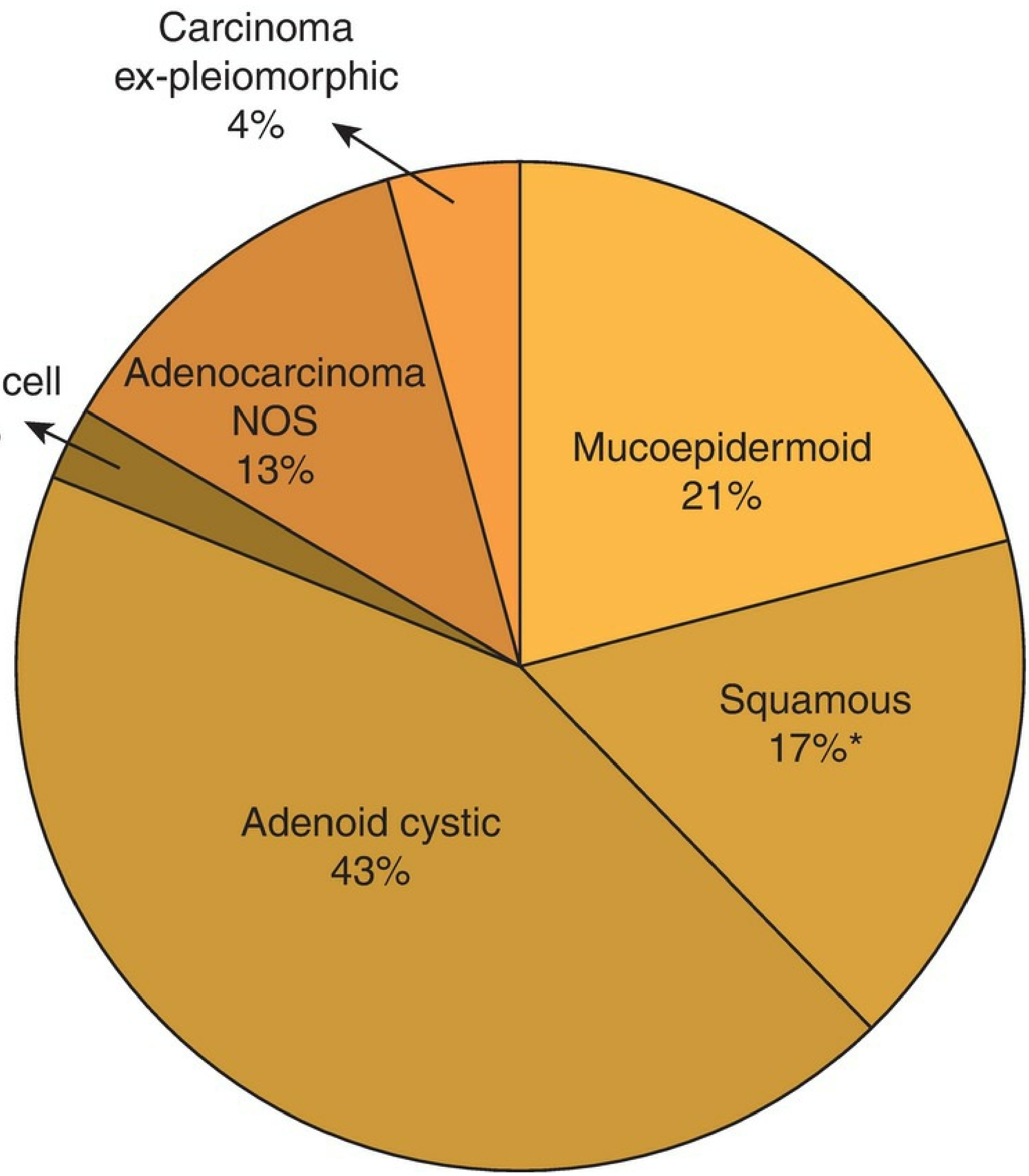
Benign Epithelial Tumors	Malignant Epithelial Tumors
Basal cell adenoma	Acinic cell carcinoma
Canalicular adenoma	Adenoid cystic carcinoma
Cystadenoma	Adenocarcinoma, not otherwise specified
Ductal papillomas	Basal cell adenocarcinoma
Intraductal papilloma	Carcinoma ex pleomorphic adenoma
Inverted ductal papilloma	Carcinosarcoma
Lymphadenoma	Clear cell carcinoma, not otherwise specified
Myoepithelioma	Cystadenocarcinoma
Oncocytoma	Epithelial–myoepithelial carcinoma
Pleomorphic adenoma	Large cell carcinoma
Sebaceous adenoma	Low-grade cribriform cystadenocarcinoma
Sialadenoma papilliferum	Lymphoepithelial carcinoma
Warthin tumor	Metastasizing pleomorphic adenoma
	Mucinous adenocarcinoma
	Mucoepidermoid carcinoma
	Myoepithelial carcinoma
	Oncocytic carcinoma
	Polymorphous low-grade adenocarcinoma
	Sebaceous carcinoma
	Sebaceous lymphadenocarcinoma
	Salivary duct carcinoma
	Sialoblastoma
	Small cell carcinoma
	Squamous cell carcinoma

Mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma, and malignant mixed tumor are the most common malignancies of the salivary glands, whereas acinic cell carcinoma and anaplastic carcinomas are encountered less frequently.[4–12,19–22] Metastases from the skin of the scalp and face and squamous variants of mucoepidermoid carcinoma should be considered and ruled out prior to making the diagnosis of a primary salivary gland squamous cell carcinoma (SCC), as those are rare. In their review, Ying et al.[23] found that SCC of the parotid represented metastases from an identified primary site in more than half of the patients. Cutaneous

carcinomas and melanomas of the scalp and face often drain into intraparotid lymph nodes and comprise 70% to 80% of metastases to intraparotid lymph nodes. Metastases from infraclavicular primary sites are less common.[24–26]

The relative incidence rates of various malignant tumors by salivary gland subsite according to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program data from 1992 to 2006 are presented in Figure 21.5. As mentioned above, perhaps erroneous SCC designation within the database may have affected the data presented in the figure. The frequency of encountering a certain neoplasm depends on the specific anatomic subsite of interest. Mucoepidermoid carcinoma is the most commonly encountered cancer in the parotid gland, whereas the submandibular gland is more likely to give rise to adenoid cystic carcinoma. Both entities occur at approximately the same rate within the minor salivary glands, followed by adenocarcinoma.


Carcinoma
ex-pleiomorphic
4%
Adenocarcinoma
NOS
13%
Mucoepidermoid,
1,326
Acinic cell
19%
Adenoid cystic
8%
Squamous
21%*
A


Carcinoma
ex-pleiomorphic
4%
Acinic cell
2%
Adenocarcinoma
NOS
13%
Mucoepidermoid
21%
Squamous
17%*
Adenoid cystic
43%
B

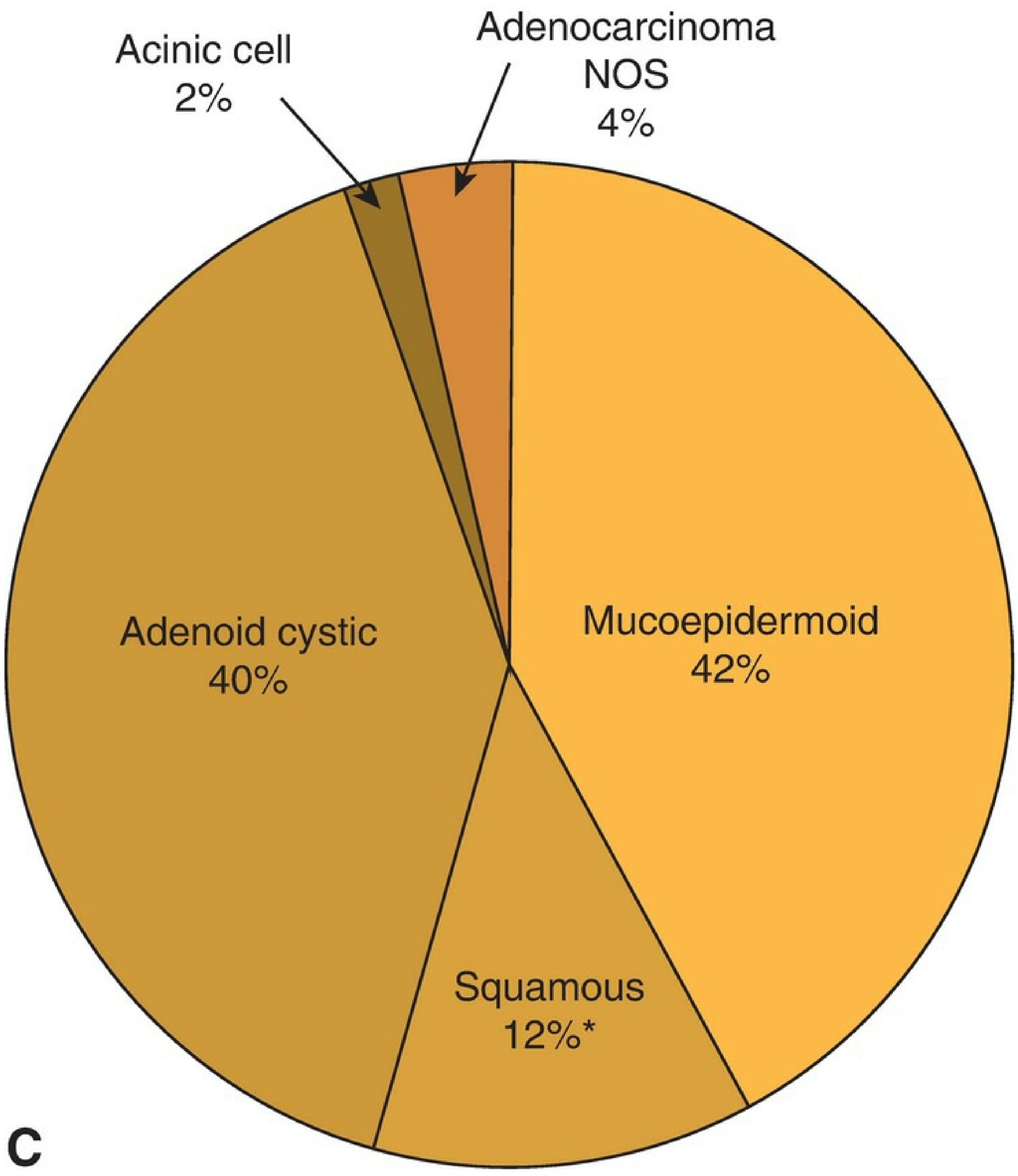


Figure 21.5 Summary of the incidence of malignant tumors of **(A)** parotid gland (4,265 cases), **(B)** submandibular glands (845 cases), and **(C)** sublingual glands (58 cases) according to the National Cancer Institute's SEER database, 1992–2006. *Authors alert the audience regarding possible misclassification of squamous cell carcinomas in the database, as the majority

of the cases are either intraparotid metastases or misdiagnosed high-grade mucoepidermoid carcinomas.

Incidence and Etiology

Approximately 7% of epithelial head and neck cancers (HNC) in the United States originate in the salivary glands.[27] The annual incidence varies between 0.3 and 3 cases per 100,000 population.[13] Similar numbers have been quoted in the European reports.[28]

Our current understanding of the pathogenesis of salivary gland malignancies is quite limited. The significance of both hereditary and environmental influences has been proposed. For example, a higher incidence of salivary gland tumors has been shown in some ethnic groups, such as Eskimos.[29] Ionizing radiation increases the risk of development of salivary gland malignancies, according to the multiple descriptive studies of atomic bomb survivors in Hiroshima and individuals with a history of low-dose radiation of the head and neck.[30–35] Industrial exposures to rubber and nickel have also been proposed to elevate the risk for development of salivary gland neoplasms.[36] Recent genomic characterizations of salivary tumors show a unique pattern of gene alterations in certain histologic subtypes. Despite these reports, a clear understanding of the etiology of salivary tumors remains elusive.

Clinical Presentation and Evaluation

History

Cancers of the major salivary glands present most commonly as an asymptomatic swelling and are often present for many months/years before a patient’s initial presentation for medical evaluation. The symptoms that arise from minor salivary gland tumors depend upon the anatomic regions involved. Thus, cancers of the paranasal sinuses can cause facial pain and/or

swelling, whereas cancers of the nasal cavity can lead to obstruction of the nasal passages and/or epistaxis. Cancers of minor salivary glands of the oral cavity can lead to a mass effect, which can result in ill-fitting dentures. Cancers arising in the larynx commonly present with hoarseness and/or sore throat. Sun exposure and the presence of current or previously excised skin lesions should be ascertained when squamous cancer or melanoma is found in parotid lymph nodes.

Pain is more common in patients with malignant compared to benign salivary gland neoplasms. Between 10% and 29% of patients with cancer of the parotid gland report pain, perhaps due to perineural invasion (PNI) by the cancer.[28,37–40] Pain is also reported in a few patients with benign submandibular neoplasms and up to 50% of patients with cancer of the submandibular gland.[8,41,42]

Physical Findings

As with any tumor, it is of paramount importance to document the exact location and size of the mass, as the details from this assessment dictate the staging, management, and treatment as well as follow-up.

As noted above, the majority of salivary tumors present as a palpable mass. Salivary lesions of the parapharyngeal space, however, may not be palpable; hence, the lateral pharyngeal walls should be examined transorally for asymmetry. Obviously, tumor fixation to either skin or deep structures suggests malignancy. In patients with untreated cancer of the parotid, fixation to the skin was reported in 9%, whereas fixation to the deep tissues was reported in 13% to 17% from the Memorial Sloan Kettering and MD Anderson Cancer Centers.[39,43]

Facial nerve involvement manifested by weakness of the muscles innervated by one or more branches of the nerve is also among the prominent hallmarks of physical examination for malignancy. Although facial nerve paresis or paralysis is present in fewer than a quarter of cases, it is generally associated with a poor prognosis.[43–45] Facial nerve involvement occurs most commonly in patients with adenoid cystic carcinoma, undifferentiated carcinoma, or SCC.[44,46,47]

The presence of cervical lymphadenopathy is another strong predictor of malignancy. Cervical lymph nodes are found to be positive at presentation in

~13% to 25% of patients with cancers of the parotid,[28,39,43,48] 14% to 33% of patients with cancer of the submandibular gland,[41,49,50] and 14% in patients with cancers of the minor salivary glands.[12] The histopathologic subtypes of cancer of the salivary glands most likely to metastasize to regional lymph nodes are SCC, high-grade mucoepidermoid carcinoma, high-grade adenocarcinoma, and malignant mixed tumor.[38,39,41]

Diagnostic Imaging

As a general principle, imaging studies should only be obtained if the patient management might be altered by the result. Most minor salivary gland tumors require radiographic evaluation to better delineate the extent of disease, including the involvement of adjacent structures. A thorough history and physical examination are generally sufficient to establish the diagnosis and extent of a tumor in the major salivary glands. Imaging is usually warranted to define the extent of the primary cancer as well as the presence of any regional metastases. This is particularly true of deep lobe parotid tumors extending into the parapharyngeal space.

Several imaging modalities are available as adjuncts in evaluating a tumor of the salivary glands. In expert hands, ultrasonography is an appropriate initial step in evaluation of the major salivary gland tumors and the status of the neck. It is readily available, none invasive, and cost-effective. Ultrasonography also allows for precise localization of the tumor within the gland and readily differentiates between cystic and solid components, thereby enabling accurate fine needle aspiration or core biopsy. Heterogeneous echogenicity, ill-defined margins, and extension beyond the borders of the gland with involvement of adjacent structures are ultrasonographic signs of a malignant process.[51–53] Computed tomography (CT) is the study of choice for the evaluation of involvement of cortical bone, whereas magnetic resonance imaging (MRI) better visualizes soft tissue details of the minor salivary gland lesions, deep parotid tumors, and perineural spread of tumor. Irregular borders, extraglandular extension, and hypointensity on T2-weighed images are suggestive of malignancy.[51,53,54] Additionally, in the case of sinonasal minor salivary gland tumors, MRI can assist in differentiating between a tumor and opacification of an obstructed sinus by fluid. Combined 18 F-fluorodeoxyglucose–positron emission tomography (FDG–PET)/CT has assumed an important role in head and neck

oncology. However, its applications remain limited in salivary gland neoplasms.[55] Although it has been shown to be superior to CT alone in delineating the tumor extent, nodal involvement, and distant metastases,[55–57] it is not particularly useful in distinguishing between malignant and benign neoplasms. This is due to the fact that some benign salivary gland lesions, such as pleomorphic adenomas and Warthin tumors, are capable of high glucose uptake.[58]

Fine Needle Aspiration Cytology

Unlike the minor salivary glands, open incisional biopsy is not recommended for parotid and submandibular glands due to the potential risk of tumor seeding and injury to the facial nerve or its branches. Fine needle aspiration cytology (FNAC) provides an insight into the preliminary diagnosis of a salivary gland lesion, which could be useful in the formulation of a management plan. For example, a poor surgical candidate may be observed once a benign result is obtained on FNAC. Additionally, a person with a diagnosis of lymphoma or benign lymphoepithelial disease of HIV on FNAC may avoid a diagnostic parotidectomy. Up to one-third of patients can be spared an unnecessary operation and risk to the facial nerve.[59]

In a recent meta-analysis of FNAC in salivary gland tumors by Schmidt et al., the sensitivity and specificity for diagnosis of neoplasia were 71% and 100%, respectively, and the sensitivity and specificity for diagnosis of malignancy were 76% and 97%, respectively. For differentiation between a benign and malignant salivary lesion, the positive and negative predictive values were 90% and 94%, respectively.[60] In a systematic review by Colella et al., the concordance rates between cytologic and surgical pathology diagnoses were 95.61% for benign and 79.95% for malignant salivary tumors. The concordance rates are lower for particular histologic types of salivary tumors: 63% for mucoepidermoid carcinomas and 70% for adenoid cystic carcinomas.[61] In summary, FNAC is a safe, fast, well-tolerated, and reliable procedure for distinguishing between benign and malignant lesions, though it is not as useful in differentiating between the various malignancies. The challenges encountered with FNAC include lack of histologic architecture within the sample and necessity of a cytopathologist with significant experience in salivary gland disease. Small-volume care center providers should maintain a low threshold for pathology consultation within

large academic institutions.

Core needle biopsy (CNB) technique was introduced to address some of the shortcomings of FNAC. Histologic architecture is preserved within the sample provided by the larger needle used (14 to 21 gauge). Also, larger tissue sample size eliminates the need for a cytopathologist to assess the specimen adequacy. Lastly, CNB specimens are formalin fixed and paraffin embedded, which facilitates the immunohistochemical staining. According to the recent meta-analysis by Schmidt et al., CNB sensitivity was 92% and specificity was 100%, with a 1.2% sample inadequacy rate. When compared to FNAC, CNB had a higher diagnostic accuracy. Hematoma was reported as the main complication, occurring in 1.7% patients, none of whom required aspiration or drainage. Theoretically, because of the larger diameter needle, CNB is more painful and there is a greater risk of facial nerve damage. No cases of permanent CN VII weakness have been reported thus far.[62] Regardless of the biopsy technique used, clinical judgment should be used in analyzing the results if the cytologic aspiration diagnosis is inconsistent with the clinical presentation.

Staging

Oncologic staging is critically important in the assessment of disease extent, prediction of prognosis, formulation of a treatment plan, and follow-up evaluations. It is an integral tool in communication between the treating surgeon and the patient and within the clinical and research medical communities. The current AJCC staging system used for major salivary gland cancers is presented in Table 21.2.[63] As of now, there is no separate standardized staging system for minor salivary cancers. A study from Memorial Hospital demonstrated that the staging system used for squamous carcinoma of the upper aerodigestive tract can be used in evaluation of the minor salivary gland malignancies arising in the same anatomic regions and has a similar prognostic value.[64]

Table 21.2 AJCC Staging System for Salivary Gland Cancer (7th Edition)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
T1	Tumor ≤2 cm in greatest dimension without extraparenchymal extension
T2	Tumor >2 cm but ≤4 cm in greatest dimension without extraparenchymal extension but <4 cm
T3	Tumor >4 cm and/or tumor having extraparenchymal extension
T4a	Moderately advanced disease. Tumor invades the skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease. Tumor invades the skull base and/or pterygoid plates and/or encases carotid artery
Regional Lymph Nodes (LN) (N)	
NX	Regional LNs cannot be assessed
N0	No regional LN involvement
N1	Metastasis in single LN <3 cm
N2a	Metastasis in single ipsilateral LN >3 cm but <6 cm
N2b	Metastasis in multiple ipsilateral LNs >3 cm but <6 cm
N2c	Metastasis in bilateral or contralateral LNs, none >6 cm
N3	Metastasis in LN >6 cm
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage Grouping	
I	T1/N0/M0
II	T2/N0/M0
III	T3/N0/M0
	T1–3/N1/M0
IVA	T4a/N0–1/M0
	T1–4a/N2/M0
IVB	T4b/any N/M0
	Any T/N3/M0
IVC	Any T/any N/M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Pathology

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common cancer of salivary gland origin. The key morphologic feature is multicystic arrangement of mucous and epidermoid cells. Based on the proportion of cystic component, neural invasion, degree of anaplasia, mitoses, and presence of necrosis,

mucoepidermoid carcinomas are classified into low-grade, intermediate-grade, or high-grade categories.[64] Low-grade cancers manifest well-defined glandular architecture. They very rarely metastasize and have an excellent overall prognosis. In high-grade mucoepidermoid carcinomas, the glandular structure is less defined or may be absent altogether. These tumors have a propensity for early and aggressive spread, with a rate of regional metastasis up to 70%.[65] As the name implies, the intermediate-grade lesions contain moderate cystic components and are less clinically aggressive than their high-grade counterparts. The patients with low-grade disease have an almost negligible recurrence rate.[66] The natural history of mucoepidermoid carcinoma is less protracted than that of other salivary malignancies; hence, a 5-year disease-free interval suggests cure.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is the most common cancer of the submandibular gland, and it is as common as mucoepidermoid carcinoma in the minor salivary glands. It constitutes ~10% of all epithelial salivary tumors. It most commonly presents as a slow-growing mass and can be associated with pain, due to its propensity for neural invasion and lack of a capsule barrier.[67] Patients with adenoid cystic carcinoma must be under careful clinical surveillance indefinitely, due to its protracted natural history, with disease-related deaths having been reported even after 20 years of disease-free survival.[68,69] Despite excellent local control, adenoid cystic carcinomas result in poor long-term outcomes due to distal recurrence. The lung is the primary site for distant metastases; however, patients can often live for many years with asymptomatic pulmonary metastases that remain stable or progress slowly.[70]

Adenoid cystic carcinoma can be arranged in solid, tubular, and cribriform histologic patterns. Predominantly, tubular and cribriform lesions tend to be less aggressive than tumors with >30% solid component.[71,72] The solid histologic pattern prognosticates development of distant metastases and poor long-term survival.[71] The difference in survival based on histopathologic grading disappears at 10 years after the treatment, suggesting that the histology affects the disease-free survival, with minimum impact on the overall outcome.[73–75]

Adenocarcinoma, Not Otherwise Specified

Adenocarcinoma, not otherwise specified (NOS), is notable for its ductal differentiation.[76] Again, histologic grading affects prognosis: high-grade lesions tend to have worse outcomes. Also, the survival decreases significantly from 5 to 10 years after treatment, which warrants a long-term surveillance in these patients.[77,78]

Salivary Duct Carcinoma

Salivary duct carcinomas (SDC) are rare tumors with aggressive clinical behavior and a poor prognosis. These cancers manifest as a rapidly growing mass and occur in patients over 50 years of age, with a male to female ratio of 4:1. The majority of cases (>80%) originate in the parotid gland.[79] The rate of cervical lymphatic involvement at presentation is over 50%. Most patients present with advanced stage disease: one-third of them suffer recurrence, 46% develop distant metastases, and 65% die of the disease, usually within 4 years of diagnosis.[80]

Carcinoma Ex Pleomorphic Adenoma

As the name implies, carcinoma ex pleomorphic adenoma originates in the setting of a pleomorphic adenoma. The malignant component usually features a poorly differentiated adenocarcinoma or an undifferentiated carcinoma. The proportions of benign and malignant components vary. This cancer is classified into noninvasive, minimally invasive, or invasive.[81] Noninvasive variants display indolent behavior similar to that of pleomorphic adenomas, whereas the invasive variants are more aggressive, with recurrence of 23%, regional metastatic rates between 49% and 56%, and distal metastatic rate up to 40%.[82,83]

Acinic Cell Carcinoma

Acinic cell carcinoma affects all age groups and is almost never seen outside of the parotid gland. Due to its indolent course, it is considered a low-grade cancer. However, high-grade papillary–cystic variants exist. Despite its overall good prognosis, the potential of local recurrence or distant metastases exists, especially in advanced stage or improperly treated tumors.[84,85] In the

review of prognostic factors by Neskey et al.,[86] older age and larger tumor size were found to correlate with poor overall survival. Also, distant metastases were prognostic of disease-specific death.

Squamous Cell Carcinoma

Primary salivary SCC of the salivary glands is rare. Time and care should be taken to distinguish it from the more common high-grade mucoepidermoid carcinoma or metastatic SCC from a cutaneous malignancy of the face, ear, or scalp. In the review by Ying et al.,[23] over 60% of patients with SCC of the parotid had a known primary cutaneous malignancy (most commonly, auricle). Only a quarter of the patients were found to have the primary salivary SCC. Both groups had high rates of cervical node involvement and poor disease outcome.

Lymphoma

Up to 85% of salivary gland lymphomas are of the non-Hodgkin type. Lymphomas of the salivary glands arise either from intraglandular lymph nodes (nodal) or from the nondiscrete lymphoid tissue within the gland parenchyma (extranodal). Although extranodal lymphomas affect salivary glands in only ~5% of cases, the overwhelming majority of these occur in the parotid gland. Lymphoma of the salivary glands either can be the only manifestation of the disease in primary cases or can also be a part of a disseminated lymphomatous process. Primary lymphomas of the salivary glands are usually associated with Sjögren syndrome.[87] Those associated with Sjögren syndrome have a significantly worse prognosis, compared to lymphomas arising in normal salivary glands. The risk of the development of the lymphoma in patients with Sjögren syndrome is 44-fold higher than that in the general population.[88]

Secondary (Metastatic) Cancers

The majority of metastases to the salivary glands involve the parotid gland and are due to intraparotid lymph node spread from the cutaneous malignancies of the face, ear, and scalp. Approximately 40% of these are

SCCs and 40% are melanomas. The majority of metastatic parotid SCCs appear within the first year of treatment. Therefore, every patient with a parotid mass with cutaneous histology should undergo careful examination of the skin of the head and neck.

Involvement of the salivary glands by the distant infraclavicular metastatic cancers is extremely rare. When it does occur, the parotid gland is most commonly affected, and the most common sites giving rise to these metastases are the lung, kidney, and breast.[89]

Grading of Malignant Salivary Gland Neoplasms

The diverse anatomic and histopathologic origins of the salivary gland cancers make them a diagnostic challenge. In order to guide the prognostic and management decision making, it was proposed to grade salivary tumors based on their clinical behavior. The association between tumor histology and local, regional, and distal control and overall outcomes has been demonstrated.[90] However, there are clinical "outliers," proving that the relationship is not absolute and constant. Seethala states that due to the rarity of cancers of the salivary glands, the grading is not standardized, which makes it less reproducible across different centers or individual pathologists with varying levels of experience in reviewing cases of cancer of the salivary glands. Also, cancers perceived as "high risk" historically, such as SDC or SCC, are not graded at all.[91]

To add to the complexity, heterogeneity even exists within the histologic groups themselves, and there are aggressive variants within the low-risk cancers as well as indolent variants among the high-risk cancers. For instance, grading is the most important consideration in prognosis and management of mucoepidermoid carcinoma. Surgical excision is sufficient for low-grade cancers, rendering an overall 5-year survival of over 90%. However, for high-grade cancers, overall survival drops below 50% and adjuvant radiation and neck dissections are required.[90,91]

The latest WHO classification of cancer of the salivary glands published

in 2005 categorizes them into low- and high-risk groups, based on the histology and grading (Table 21.3). To fine-tune the existing system, Jouzdani et al.[92] demonstrated a separate intermediate-risk category. Based on the constructed Cox models, this intermediated group has an individual prognostic value: One step elevation from low- to intermediate- to high-risk level resulted in 2.3 increase in the risk of disease recurrence and 2.6 increase in risk of nonspecific death. This three-tier histologic classification is presented in Table 21.4.[92]

Table 21.3 Risk Classification of Cancer of the Salivary Glands by the WHO

Low Risk	High Risk
Acinic cell carcinoma Adenocarcinoma NOS and cystadenocarcinoma, low grade[a] Basal cell adenocarcinoma Carcinoma ex pleomorphic adenoma (intracapsular/minimally invasive or with low-grade histology) Clear cell carcinoma Epithelial–myoepithelial carcinoma Low-grade mucoepidermoid carcinoma[a] Low-grade salivary duct carcinoma (low-grade cribriform cystadenocarcinoma) Myoepithelial carcinoma Oncocytic carcinoma Polymorphous low-grade adenocarcinoma Sialoblastoma	Adenocarcinoma and cystadenocarcinoma, NOS, high grade[a] Adenoid cystic carcinoma[b] Carcinoma ex pleomorphic adenoma (widely invasive or high-grade histology) Carcinosarcoma High-grade mucoepidermoid carcinoma[a] Large cell carcinoma Lymphoepithelial carcinoma Metastasizing pleomorphic adenoma Mucinous adenocarcinoma Sebaceous carcinoma and lymphadenocarcinoma Squamous cell carcinoma Small cell carcinoma Salivary ductal carcinoma

[a]For these tumors, intermediate-grade classification is controversial. For mucoepidermoid carcinoma, it depends on the grading system employed. For adenocarcinoma NOS (not otherwise specified), intermediate grade should be placed in the high-risk group.

[b]All adenoid cystic carcinoma grades are high risk for local recurrence, but only solid high-grade adenoid cystic carcinoma is high risk for nodal metastasis.

Table 21.4 Three-Tier Histologic Classification of Cancers of the Salivary Glands by Jouzdani et al.

Low Risk	Intermediate Risk	High Risk
Acinic cell carcinoma Basal cell carcinoma Clear cell carcinoma Cystadenocarcinoma Epithelial–myoepithelial carcinoma Low-grade cribriform cystadenocarcinoma Low-grade mucoepidermoid Polymorphous low-grade adenocarcinoma Mammary analogue secretory carcinoma	Mucinous adenocarcinoma Myoepithelial carcinoma Intermediate-grade mucoepidermoid Tubular and cribriform adenoid cystic carcinoma	Adenocarcinoma NOS Carcinosarcoma Dedifferentiated acinic cell carcinoma Dedifferentiated basal cell adenocarcinoma High-grade mucoepidermoid Large cell carcinoma Lymphoepithelial carcinoma Oncocytic carcinoma Salivary duct carcinoma Sebaceous carcinoma Small cell carcinoma Squamous cell carcinoma Undifferentiated, solid adenoid cystic carcinoma

NOS, not otherwise specified.

Molecular Alterations in Salivary Malignancy

The goal of analysis of molecular oncologic details is to identify diagnostic biomarkers and markers prognostic of clinical behavior and to broaden the spectrum of potential therapeutic targets and therapies. HER2 is a transmembrane glycoprotein receptor involved in cell growth and differentiation that has been very well studied in breast oncology due to its overexpression in aggressive breast carcinoma. HER2 was commonly found to be overexpressed in cancers of the salivary gland of excretory duct origin, such as SDC and mucoepidermoid carcinoma.[93–96] Cancers with HER2 overexpression have a propensity for regional lymphatic spread and were shown to have a worse overall survival.[97] Unfortunately, the clinical benefit of HER2-targeted therapy has not yet been demonstrated.[98,99]

The epidermal growth factor receptor (EGFR) is another transmembrane receptor involved in signal transduction. Its expression has also been correlated with aggressive malignant behavior.[100] EGFR is commonly encountered (>50% frequency) in both mucoepidermoid carcinoma and SDC but is not seen as commonly in adenoid cystic carcinoma.[41,97,101–181]

C kit is a protooncogene responsible for encoding a transmembrane receptor–type tyrosine kinase, which is involved in growth stimulation and differentiation. Its expression has been demonstrated in adenoid cystic carcinomas.[102,103] Absence of C kit expression is a poor prognostic factor.[100]

Additionally, a number of genetic alterations were identified in cancer of the salivary glands over the last decade. Translocation t(11:19)(q21;p13) results in the MECT1–MAML2 fusion gene, which disrupts the NOTCH pathway in mucoepidermoid carcinoma, and its presence carries a favorable prognosis.[104] Translocation t(6;9)(q22-23;p23-24) produces a fusion of transcription factors MYB and NFIB in adenoid cystic carcinoma and has been correlated with worse outcomes.[105]

More recently, complete genomic profiling of adenoid cystic carcinoma revealed extensive mutational diversity of this disease, providing some answers to the questions of oncogenesis and tailored treatment. For example, mutations in genes responsible for chromatin-state regulators were identified, which may suggest chromatin deregulation as the inciting event for carcinoma development.[106,107] Additionally, multiple "actionable genomic alterations" (sequences known to impact targeted oncologic treatment) were identified in over 40% adenoid cystic carcinoma tumor samples.[108]

Treatment: Surgery

Surgery remains the gold standard of treatment of salivary gland malignancies. The next few paragraphs will review the details of surgical management for both major and minor salivary glands, indications for neck dissection, and usefulness of intraoperative frozen section analysis.

Parotid Gland

A general thought process when considering treatment options for patients with cancer of the salivary glands is summarized in Table 21.5. Surgery remains the primary treatment modality for primary and/or regionally metastatic cancer of the parotid gland. The minimum operation appropriate for early-stage cancers is lateral or superficial parotidectomy with dissection and preservation of the facial nerve. More extensive cancers may require more extensive operations with resection of adjacent structures, such as portions of the mandible, zygoma, temporal bone, overlying skin, and facial nerve. In general, these radical procedures are associated with poor oncologic outcomes.

Table 21.5 General Algorithm for Management of Cancer of the Salivary Glands

Surgery: Primary Site Only	Low-grade histology Low T stage (T1 or T2)
Primary Site and Neck Dissection	Pathologic cervical LNs N0 neck in setting of: High-grade histology High T stage (T3 or T4)
Surgery and Adjuvant XRT	Close (<2 mm) or positive margins High-grade histology High T stage (T3 or T4) Pathologic cervical lymph nodes Perineural invasion
Chemotherapy	Distant metastasis or unresectable disease

The introduction of radiation has altered our approach to the management of the facial nerve in surgical treatment of parotid cancers. Unless there is gross infiltration of the nerve by the tumor, every attempt at preservation should be made.[109] Radiotherapy in the adjuvant setting is intended to control any microscopic residual disease. When planning the management of the facial nerve, histologic characteristics of the cancer must be taken into consideration. This is particularly true of cancers with a propensity for PNI and spread, such as adenoid cystic or SCC. Per review by Iseli et al.,[110] better 5-year disease control and a trend for improved 10-year survival were observed in patients with adenoid cystic carcinoma who underwent facial nerve sacrifice. As expected, this came at the expense of quality of life.[110] If the main trunk of the nerve or its major branches must be sacrificed and primary anastomosis is not feasible, cable grafting with the greater auricular or sural nerves should be performed in the same setting. As mentioned above, over 60% of patients with facial nerve grafting are able to achieve the best outcome, defined as House-Brackmann Grade III. Most Grade III and Grade IV recoveries occur within 6 months.[111] Positive nerve margins do not affect the postoperative facial nerve function after immediate grafting in the review by Wax and Kaylie; hence, the repair is recommended even when perineural margins are suspected to be positive.[112] According to Brown et al.,[113] a

comparison of radiated and unradiated grafts revealed no significant difference with respect to the best facial nerve function achieved.

Submandibular and Sublingual Glands

En bloc resection of the entire submandibular triangle for cancer of the submandibular gland has been popularized in the earlier literature.[41] Currently, the extent of resection is being individualized to the tumor and patient characteristics. For small early-stage cancers confined to the submandibular gland, a simple excision of the gland may be adequate. For a more extensive cancer, a more anatomically aggressive operation may be needed with resection of the adjacent lymph nodes, overlying skin, nearby muscles, lingual and/or hypoglossal nerve(s), bone, and the floor of the mouth.

With respect to sublingual glands, en bloc resection is preferred. The extent of such resection is a balance between optimal oncologic result and optimal functional outcome. In general, the principles of SCC management are followed.

Minor Salivary Glands

The surgical approach to the management of cancer of minor salivary origin is location specific. Again, the principles of management of SCC of the upper aerodigestive tract are followed. An individualized and tailored to the patient and tumor characteristics surgical approach and operation are chosen.

Neck Dissection

Metastases of cancer of the salivary glands to the regional lymph nodes have an adverse impact on prognosis.[114] A recent analysis of the anatomical distribution of cervical lymph node involvement in cancer of the parotid concluded that unilateral cervical lymph nodes in levels II and III are at greatest risk for metastasis.[115] The risk of cervical metastases depends on the tumor location, size, and grade. For cancers of the major salivary glands, the reported rates of cervical lymphatic involvement are between 14% and 25%.[116–119] This range is much broader for cancers of the minor salivary glands. Although cervical metastases are present in 10% of cancers arising within minor salivary glands of the oral cavity, this number rises to 33% for

pharyngeal and laryngeal sites of origin.[120] Larger cancers have a higher incidence of cervical lymphatic involvement: the rate of occult cervical metastases is 20% in patients with a cancer >4 cm in size and only 4% in those with smaller lesions.[118] Finally, the rates of positive cervical lymph nodes are between 32% and 62% in high-grade cancers of major salivary glands and 40% in minor salivary gland cancers.[116–120] Low-grade histopathology tumors of both minor and major salivary glands harbor cervical lymph node metastases in <15% of cases.[116–121]

Although there is a clear indication for cervical lymphadenectomy in patients with palpable neck disease, there are no uniformly accepted guidelines for management of a clinically negative neck. The histology of the cancer and its anatomic dimensions determine the rate of occult metastases. Zbaren et al.[122] demonstrated that patients who underwent an elective neck dissection versus observation for parotid carcinoma had lower recurrence rates (12% vs. 26%) and better 5-year disease-free survival (86% vs. 69%). Herman et al.[120] treated 59 clinically N0 high-grade cancer of the salivary gland with surgery and postoperative radiation to the primary site and elective neck dissection or neck irradiation. After a 5.2-year follow-up, the rates of recurrence and cause-specific survival were similar.[120] This suggests that elective neck treatment, surgical or with irradiation, should be offered to patients with large and high-grade cancers.

Intraoperative Frozen Section Analysis

Advocates of the intraoperative use of frozen section pathologic analysis in surgery for cancer of the salivary glands find it useful in planning of the extent of local resection and the need for elective neck dissection. A recent meta-analysis of 13 studies with over 1,800 cases by Schmidt et al.[123] demonstrated sensitivity of 90% and specificity of 99% for frozen section analysis. The accuracy of the analysis was found to be consistent across a number of study centers.[123] However, the accuracy of frozen section is histopathology dependent: it is somewhat lower for malignant lesions at 85.9%, compared to 98.7% in benign pathology cases. The most common overdiagnosed benign tumor is pleomorphic adenoma. Mucoepidermoid carcinoma is the most frequently encountered entity in the false-negative category.[13] In summary, frozen section pathologic analysis may be useful in operative decision making in challenging settings. However, the findings of the analysis should be considered in light of the clinical picture and caution should be taken if there is a discrepancy.

Results of Surgical Treatment

For patients treated with surgery alone, failure at the primary site has been a challenge. Prior to the introduction of adjuvant radiation, the reported rates of locoregional recurrence were 49%, 60%, and 65% for parotid, submandibular, and minor salivary gland primary sites, respectively. Isolated failure in the neck was quite rare.[4]

Overview of Surgery and Complications for Cancer of the Parotid and Submandibular Glands

Superficial Parotidectomy

The patient should be prepped and draped in such a way that half of the face

is exposed, so that facial motion can be monitored during the procedure. Muscle paralysis should be avoided for the same reason. A modified Blair incision is outlined: anterior to the tragus, around the earlobe, and into the submandibular crease or into the hairline. Markings should be made at the site of earlobe attachment, which would facilitate closure later. The skin is elevated over the parotid containing the mass, taking care to preserve the adequate flap thickness. The parotid gland is elevated off of the ear canal and the anterior border of the SCM muscle. The main trunk of the facial nerve is identified between the insertion of the digastric muscle and tragal pointer. Each of the branches of the facial nerve is dissected, elevating the parotid gland substance off of the nerve. The face should be cautiously monitored for movement. Every effort should be made to preserve the facial nerve, except for the cases where preoperative facial paralysis exists. Postoperative hemostasis and facial nerve function need to be confirmed. The wound is closed in layers over a suction drain. The further surgical details and descriptions of more extensive procedures are beyond the scope of this chapter.

Submandibular Gland Excision

Adequate exposure can be achieved by cervical extension. The patient should be prepped and draped in such a way that the lower lip is exposed, so that facial motion can be detected during the procedure. Muscle paralysis should be avoided for the same reason. A horizontal incision is made within the natural neck crease approximately at the level of hyoid bone. The incision is carried through skin, subcutaneous tissues, and platysma muscle to the most inferior extent of the submandibular gland. The glandular fascia is incised and elevated off the gland. Facial vein is encountered and ligated. Vein retraction and fascia elevation will protect marginal mandibular nerve, which is superficial to both of these structures. The superior portion of the gland is dissected off of the mandible bluntly. The anterior portion of the gland is identified and separated from the anterior belly of digastric muscle. Once the mylohyoid muscle is identified, it is skeletonized to its most posterior extent and retracted medially to expose the duct and lingual and hypoglossal nerves. Only once both nerves are exposed, and in view, the duct is divided. The rest of the gland is delivered from the neck quite easily. The wound is closed in layers over a suction drain. The further surgical details and descriptions of more extensive procedures are beyond the scope of this chapter.

Complications of Parotidectomy

Injury of the facial nerve is the most feared and devastating complication of parotidectomy. To establish the baseline presence and degree of weakness, facial function should be assessed once the patient is extubated and able to follow commands. Some degree of facial weakness is expected in 13% to 100% of patients undergoing parotidectomy, depending on the underlying pathology and its location within the gland, extent of operation, and whether it is a reoperative setting.[124] Most cases of facial nerve dysfunction are a result of stretching, entrapment, compression, and thermal and ischemic injuries.[125] The factors predictive of postparotidectomy facial nerve paresis are extent and duration of operation, close proximity of the tumor to the facial nerve, histologic makeup, and the size of the lesion.[126,127] Fortunately, the rate of permanent paralysis is below 5%, with most cases of facial nerve weakness recovery occurring within 12 months of operation.[124,126,127] Should the facial nerve be transected, inadvertently or as a planned step, primary tension-free repair with fine permanent interrupted sutures under magnification should be attempted first.[128] If tension-free repair is not feasible, greater auricular or sural nerves can be used as the interposition grafts. Over 60% of patients with facial nerve grafting are able to achieve facial symmetry at rest, which is the best outcome obtainable after grafting. Most paretic nerves recover within 6 months.[111] Eisele et al.[125] found that the majority of the otolaryngologists/head and neck surgeons in the United States and the United Kingdom routinely use nerve monitoring during parotid surgery. Although it can be of great benefit in technically demanding situations, such as a reoperative setting, radiated field, distorted anatomy, or minimally invasive procedures, there is minimal evidence supporting its routine use in all cases of parotid gland tumor surgery.[125] To reduce the risk of facial nerve injury, alternative dissection techniques should be considered in challenging operative situations. The facial nerve can be identified in the mastoid bone in cases of tumor extension into the region of the stylomastoid foramen. Alternatively, a retrograde dissection should be performed if the main trunk of the facial nerve cannot be dissected in a safe manner.

Hemorrhage is another serious perioperative complication. Most occur within 24 hours and are typically due to failure to achieve adequate

intraoperative hemostasis.[129] Prescription and over-the-counter agents may produce anticoagulation and antiplatelet activity, which increases the risk of bleeding and should be discontinued a sufficient time period before the surgery. Once the diagnosis of the hematoma is established, urgent exploration and evacuation must be performed.

Sialocele, another type of surgical bed collection, may occur after parotid surgery. The transected edge of the parotid gland may secrete saliva and collect under the skin (sialocele) or drain through the skin (fistula). As expected, the intensity of drainage is correlated to gustatory stimuli. The incidence of this bothersome complication is between 4% and 14%.[130,131] The condition is usually self-limited and resolves with repeated needle aspiration and compression dressings. Oral anticholinergics may be useful and should be considered for their suppressive effect on the salivary flow. Should the conservative measures fail, more radical surgical interventions, such as tympanic neurectomy, botulinum toxin A injection, and completion parotidectomy, should be explored.[132]

Frey syndrome (gustatory sweating) is a common occurrence after a parotidectomy. It results from the aberrant healing of transected parasympathetic secretomotor fibers supplying the parotid gland and sympathetic fibers supplying the cutaneous sweat glands and blood vessels, which in turn produces sweating and flushing with gustatory stimuli. The incidence of the condition varies according to the method of detection used. For instance, between 43% and 96% of patients who have had a parotidectomy test positive with a starch–iodine (Minor) test. However, only 14% to 43% of patients report clinical symptoms, most on average within 5 months postoperatively. Less than 10% of postparotidectomy patients experience intractable gustatory sweating.[133,134] Once the syndrome is diagnosed, it can be managed with topical antiperspirants or superficial botulinum toxin A administration.[135] However, most surgeons aim for prevention of clinically evident disease. Intraoperative techniques, such as SMAS, superficial temporal artery fascial (STAF) and SCM flaps, and AlloDerm interpositional grafts, have been described.[136–139] A recent meta-analysis by Curry et al.[140] confirmed the benefit of preventive intraoperative techniques.

Hypoesthesia of the greater auricular nerve is a consequence, not a

complication of parotidectomy. The numbness of the ear lobe and surrounding area resolves to a various degree within 1 year of the operation. Preoperative counseling regarding this sequela of surgery is recommended. Suggestions of preservation of the posterior branches of the greater auricular nerve have been made in hopes of a faster and more complete recovery.[141]

Alteration of the lateral facial contour as a result of parotid excision is of esthetic importance. Again, it is an expected consequence of the operation, not a complication; nonetheless, it can be quite disturbing to the patient. A variety of flaps (SMAS, STAF, SCM), grafts (AlloDerm and dermofat), and lipofilling techniques have been shown to reduce the postparotidectomy depression in the preauricular and over the angle of mandible.[136–139,142] Unless a radical procedure was performed, the majority of the defects take on a more natural contour in a course of a few months.

Complications of Resection of the Submandibular Gland

As with parotid surgery, operations on the submandibular gland place the facial nerve at risk of injury; the marginal mandibular branch is the most commonly affected. The clinical manifestation of the injury ranges between a minor cosmetic asymmetry with movement of the corner of the mouth and poor oral competence. The incidence of transient and permanent weakness is ~9% and <1%, respectively.[143] As mentioned earlier, other nerves in the proximity are the lingual and hypoglossal. A theoretical possibility of injury exists at the time of Wharton duct ligation. Transient lingual nerve paresthesia was noted in 2% by Preuss et al.[143] in their 15-year experience.

Treatment: Radiation Therapy

Traditionally, salivary gland cancers were thought not to be amenable to radiation, but over the last two decades, evidence of the opposite was revealed and radiation became an important treatment modality in both primary and adjuvant settings.[144] Radiotherapy has been shown to improve local–regional control and disease-free survival postoperatively in high-grade and/or advanced stage tumors and those with close or involved margins. Evidence regarding the effect of radiation on the overall survival remains inconclusive. In cases of recurrence after radiation, distant metastasis is the predominant site of failure.[145–147] The Head and Neck Service at Memorial Sloan Kettering Cancer Center performed a matched pair analysis of patients treated with and without adjuvant radiotherapy. Patients with stage III and IV cancer who received postoperative radiation had improved local control and better survival. Patients with early-stage cancer did not benefit from the adjuvant radiation.[148] The summary of current indications for postoperative radiotherapy in the treatment of salivary cancer is presented in Table 21.6.

Table 21.6 Indications for Adjuvant Radiotherapy

High-grade histology
Advanced stage
Close/positive margins
Perineural invasion
Recurrent disease
Pathologically confirmed positive cervical lymph nodes

An alternative beam energy, fast neutron radiation, offers a biologic advantage specific to the treatment of adenoid cystic carcinoma. It has been used for recurrent or residual disease in anatomically challenging to access locations, such as the skull base. Morbidity related to neutron therapy remains an area of investigation and a significant concern, and the initial enthusiasm for its use in the primary treatment of cancer of the salivary glands has waned.[149,150]

In addition to its important role as an adjunct, radiotherapy has been used in the primary setting for patients who are in inoperable or medically unstable. The radiation doses used range between 57 and 74 Gy. Complete responses at 12 months have been reported in a sizeable proportion (64.7%) of patients.[151] Longer follow-up, however, has demonstrated 10-year local control, overall and metastasis-free survival rates of 57%, 46%, and 67%, respectively.[152]

The toxicities of radiation therapy include xerostomia, dysphagia, osteoradionecrosis, and skin and soft tissue fibrosis. In addition, patients treated for cancer of the parotid appear to be particularly prone to sensorineural hearing loss and cochlear damage as a result of adjuvant or primary radiation. Intensity-modulated radiotherapy (IMRT) has been shown to reduce the radiation dose delivered to the cochlea as compared to the conventional three-dimensional conformal radiotherapy (3DCRT).[153] A phase III study of cochlear-sparing IMRT is now open in hopes to compare IMRT and standard 3DCRT with the hearing loss as the primary endpoint.[154]

Treatment: Chemotherapy

Systemic therapy for salivary gland malignancies is used in a palliative setting in patients with bothersome symptoms or rapid disease progression. The available data are limited to some phase II trials in adenoid cystic carcinoma and retrospective reports from individual institutions. There are no phase III trials.[155]

Monotherapy usually involves cisplatin or 5-fluorouracil. Most analyses include a very small number of patients encompassing a variety of histologies. The response rates vary widely between 10% and 70%, and they are typically short-lived.[155] The largest phase II study included 25 patients treated with cisplatin. The response rates were between 16% and 21% in patients without distant site involvement. The rates in the patients with metastatic disease were even lower. The response duration was limited to between 5 and 9 months.[156] Adenoid cystic carcinoma appears to be sensitive to 5-fluorouracil. The response rates and duration reported between 30% and 46% and between 5 and 24 months, respectively.[157,158]

Combination chemotherapy has been shown to result in better response rates, but there has been limited survival benefit. In very symptomatic patients, initial platinum and doxorubicin combination is preferred. Licitra et al.[159] reported the overall response of 27% in their phase II study of 22 patients treated with cyclophosphamide/doxorubicin/cisplatin combination.

The results of molecular targeted therapy have been rather disappointing thus far. There have been no objective responses noted with tyrosine kinase inhibitors (imatinib, gefitinib, lapatinib), monoclonal antibodies (cetuximab, trastuzumab), or proteasome inhibitor bortezomib.[99,160–165] In the best response cases, disease stabilization for a few months was achieved.[155] Thus far, there have been no trials comparing conventional and novel chemotherapy agents as of yet. Currently, over 100 trials are actively recruiting patients with cancer of the salivary gland.[166]

Treatment: Chemoradiation

Although surgery remains the standard of care for treatment of salivary gland malignancies, concurrent chemoradiation options have been explored in patients with locally advanced and unresectable tumors. Rosenberg et al.[167]

report 2-year overall survival and disease-free survival of 67% and 44%, respectively, in patients with advanced high-grade disease (mostly mucoepidermoid carcinoma). Patients undergoing chemoradiation for adenoid cystic cancers seem to be doing even better, with 5-year overall survival and local progression-free survival of 87% and 61%.[168]

Prognostic Factors

Clinical stage is the strongest predictor of prognosis in both major and minor salivary gland cancers.[47] Similar results have been reported by other major centers internationally. The multivariate analysis from the United Kingdom confirmed clinical stage as the most important independent prognostic factor, with 10-year survival rates of 96%, 70%, 47%, and 19% in patients with AJCC stage I through IV disease, respectively.[169] A study from Denmark of patients with parotid cancer revealed similar survival rates of 85%, 69%, 43%, and 14% for UICC stage I through IV, respectively.[28]

Prognosis and treatment outcome strongly correlate with the tumor histopathologic type and grade.[42,148,169] In general, patients with high-grade histologic type present with advanced stage lesions, so histologic grade is at least partially reflected in the clinical stage. Patient with acinic cell carcinoma tend to do very well with a 5-year survival of 76% to 100%.[84,85,170] In patients with mucoepidermoid carcinoma, 5-year survival drops from 76% to 100% in patients with low-grade lesions to 22% to 49% in patients with high-grade lesions.[171–176] In adenoid cystic carcinoma, 5-year survival ranges between 50% and over 80%, with solid component histology having worse outcomes.[68–75,177–180] Long-term survival is dramatically worse: 10-year survival is between 29% and 67%, and 15-year survival is at 25%.[68,69] The overall 5-year survival for patients with salivary adenocarcinoma is 76% to 85% but falls to 34% to 71% after 10 years.[76]

Patient demographic details, such as gender and age, are also important prognostic factors. Males tend to have a worse outcome.[181] Increasing age negatively affects the outcome prognosis.[42,136]

Summary

Salivary gland malignancies are a relatively rare and histologically heterogeneous group. Arising from both major and minor salivary glands, they present at various anatomical sites and demonstrate a wide range of clinical behaviors. Both diagnostic imaging and fine needle aspiration help to establish the plan of care. Prognostic factors include clinical stage, histopathologic type and grade, age, and gender. Although surgery, in form of excision of the primary tumor with or without cervical lymphadenectomy, remains the gold standard, other modalities (such as definitive radiation or concurrent chemoradiation) are available options in unresectable cases.

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22 Tumors of the Parapharyngeal Space

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The evaluation and treatment of tumors of the parapharyngeal space (PPS) have evolved over the past few decades. Successful management of tumors in this region is now a multidisciplinary endeavor encompassing a broad range of medical and surgical subspecialty knowledge. There is an increasing awareness of the need to balance the benefits of surgical resection with the anticipated functional deficits and subsequent morbidity that can occur following surgical intervention. An intimate understanding of the anatomy of this region remains the key factor in surgical planning and successful management of tumors involving this anatomic region.

ANATOMY

The PPS is a potential space deep in the neck, shaped like an inverted pyramid. The borders delineating this space are made up of both immobile and distensible tissues, which has implications on the directions of growth and eventual clinical presentation of tumors occurring in this space. At its superior limit, representing the base of the inverted pyramid, is a small region of the temporal and sphenoid skull base including the carotid canal, jugular foramen, and hypoglossal foramen. The inferior limit representing the apex is at the level of the greater cornu of the hyoid bone. The medial borders of this space are the pharyngeal constrictor muscles of the oropharynx, a distensible plane that enables tumor expansion. The medial pterygoid muscle, ramus of the mandible, and the deep lobe of the parotid gland represent the lateral borders, whereas the prevertebral fascia and cervical vertebrae make up the posterior border. The superior, lateral, and posterior borders are relatively

immobile barriers, and as such, tumor growth typically occurs in either the medial or inferior direction leading larger tumors involving these areas to manifest as a pharyngeal mass or cervical mass.

The PPS has traditionally been divided into prestyloid and poststyloid compartments by the fascial band connecting the styloid process and skull base to the tensor veli palatini muscle (Fig. 22.1). The prestyloid space, positioned anterolaterally, is a potential space composed of adipose tissue, lymph nodes, minor salivary glands, branches of the mandibular division of the trigeminal nerve, internal maxillary artery, and the pharyngeal venous plexus. The poststyloid space, positioned posteromedially, contains the carotid artery, internal jugular vein (IJV), cranial nerves IX to XII, the sympathetic chain, and lymph nodes. In relation to other neck spaces, both the masticator and parotid spaces are located anterolaterally, whereas the retropharyngeal space is located posteromedially. Recently, a suggested update to the nomenclature of the PPS refers to the prestyloid space as the true PPS, whereas the poststyloid space is referred to as the vascular space.[1]

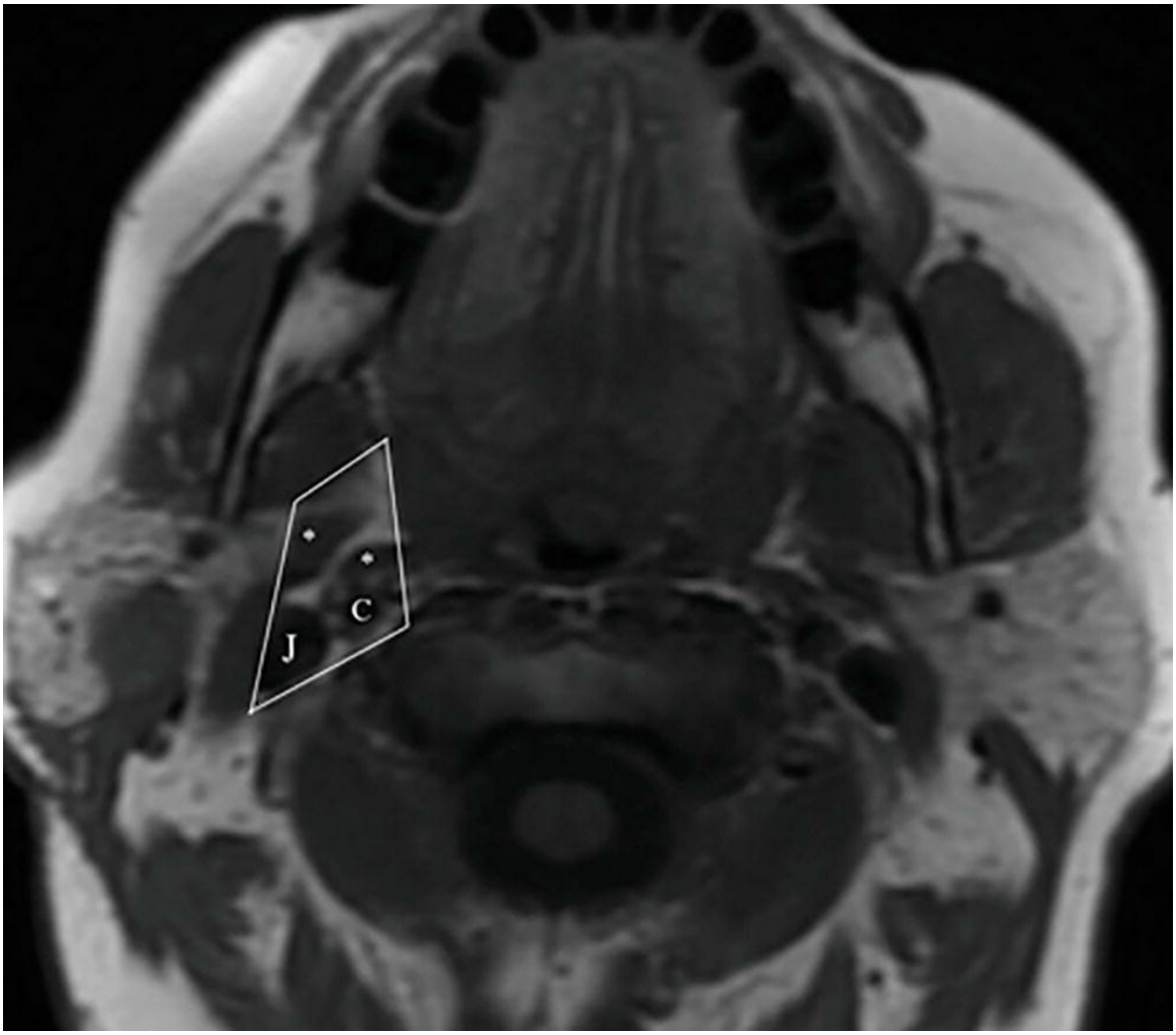

Figure 22.1. Normal anatomy. The PPS is separated into a prestyloid and poststyloid compartment by the styloid process and styloid musculature (*asterisk*). The prestyloid compartment is primarily composed of adipose tissue, which demonstrates high signal intensity on this T1-weighted MR image. The poststyloid compartment contains the carotid sheath and its contents, the internal jugular vein (*J*), and carotid artery (*C*). The poststyloid compartment is also referred to as the carotid space or vascular space.

CLINICAL PRESENTATION

The vast majority of patients with a mass in the PPS have little to no symptoms until the size of the mass is sufficiently large. This is due in part to the relatively slow growth of tumors that arise in this area. Therefore, it is not

surprising that many of these masses are found as incidental findings on imaging studies performed for other reasons. Nonetheless, there are multiple symptoms that may be related to tumors arising within the PPS reflecting the diverse pathology that can arise from within this region. These can be categorized broadly into symptoms related to tumor mass effect or tumor invasion such as functional deficits from cranial nerve involvement. Natural expansion of tumor along the path of least resistance along the medial boundary leads to displacement of the lateral pharyngeal wall and tonsil that may manifest as dysphagia, dysarthria, new-onset snoring, voice changes, or an ill-fitting maxillary denture due to soft palate displacement of the tumor. Tumors narrowing the oropharyngeal region may lead to symptoms of obstructive sleep apnea.[2,3] Hearing loss can arise from middle ear effusion by compression of the cartilaginous portion of the eustachian tube, whereas the presence of trismus implies infiltration of the pterygoid musculature or impingement on the coronoid process of the mandible. Tumors arising in the superior portion of the PPS in close proximity to the skull base may cause manifestations of a jugular foramen syndrome characterized by nerve palsies of cranial nerves IX, X, and XI. Extension of tumor along an inferior plane can lead to a palpable cervical mass posterior and inferior to the angle of mandible or tail of the parotid. Involvement of cranial nerves or the cervical sympathetic chain may cause symptoms of dysphonia from vocal cord paralysis or paresis, dysarthria from tongue weakness, or Horner syndrome.

DIAGNOSTIC CONSIDERATIONS

Diagnostic Imaging

As mentioned above, many PPS masses are discovered incidentally on imaging studies that include the head and neck region. However, the preferred radiologic modality in the assessment of PPS tumors is magnetic resonance imaging (MRI) with gadolinium enhancement as it allows for precise localization of tumors in relation to surrounding neurovascular and muscular structures, thus helping to differentiate between benign and malignant masses. T1 sequences are useful for defining the interaction between the tumor and surrounding fat planes, whereas T2 sequences delineate the relationship between tumor and adjacent muscle. Postcontrast T1 imaging allows for assessment of perineural spread. The use of particular

MRI sequences including phase contrast angiography, time of flight, and MR angiography have been shown to increase the diagnostic sensitivity and specificity of PPS lesions.

Although MRI remains the preferred modality, newer multidetector CT scanning has a number of advantages including quicker scanning times, improved spatial resolution up to 0.082 mm^3 (compared to 4.4 mm^3 for T1-weighted images and 1.1 mm^3 for time of flight MR angiography), and ability for multiplanar reconstruction of images.[4] Quicker scanning times of <30 seconds make images less susceptible to motion artifacts compared to MRI and should be a consideration in patients who are not candidates for MRI or experience claustrophobia. There are considerable cost savings with CT scan compared to MRI as well. Ultrasound is an inexpensive, noninvasive, nonionizing radiation diagnostic modality that has the added advantage of enabling radiologic guidance for fine needle aspiration biopsy (FNAB).

The diagnosis of a tumor within the PPS can be predicted based on a distinction made on its location within either the prestyloid or poststyloid space. The majority of tumors found within the prestyloid compartment are of salivary gland origin, whereas in the poststyloid compartment, tumors of neural origin constitute the majority of lesions. The determination of whether a tumor is located in the prestyloid or poststyloid space is based on a number of factors including tumor position relative to the carotid artery, styloid process, medial pterygoid muscle, and parapharyngeal adipose tissue plane. In prestyloid masses, the carotid artery is posteriorly displaced, the medial pterygoid muscle is anterior in relation to the tumor, and the parapharyngeal adipose tissue plane will be located along its medial aspect. In poststyloid masses, the carotid artery is displaced anteriorly, whereas the parapharyngeal adipose tissue is displaced in an anterolateral direction (Fig. 22.2). As a poststyloid mass expands laterally, it will extend posterior to the styloid process.

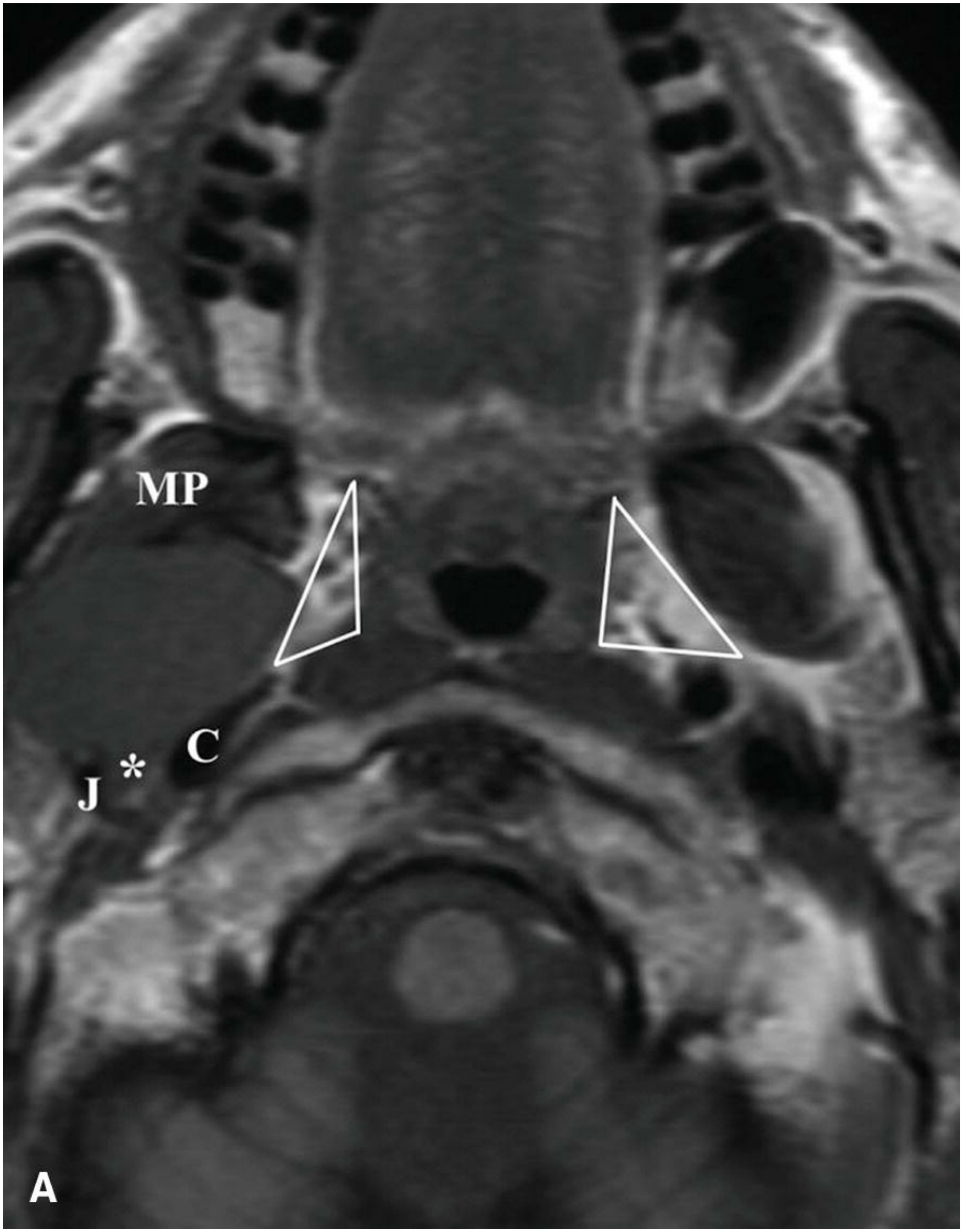
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Figure 22.2. Typical prestyloid **(A)** and poststyloid **(B)** parapharyngeal tumors. **A:**Prestyloid pleomorphic adenoma displaces the medial pterygoid

muscle (*MP*) slightly anteriorly and the prestyloid parapharyngeal adipose tissue (outlined) medially, whereas the carotid artery (*C*) is posteriorly located. **B:**Poststyloid vagal paraganglioma displaces the carotid artery (*C*) anteriorly and the prestyloid parapharyngeal fat (outlined) anterolaterally. (*C*, carotid artery; *J*, internal jugular artery; *asterisk* denotes styloid musculature.)

Fine Needle Aspiration Biopsy

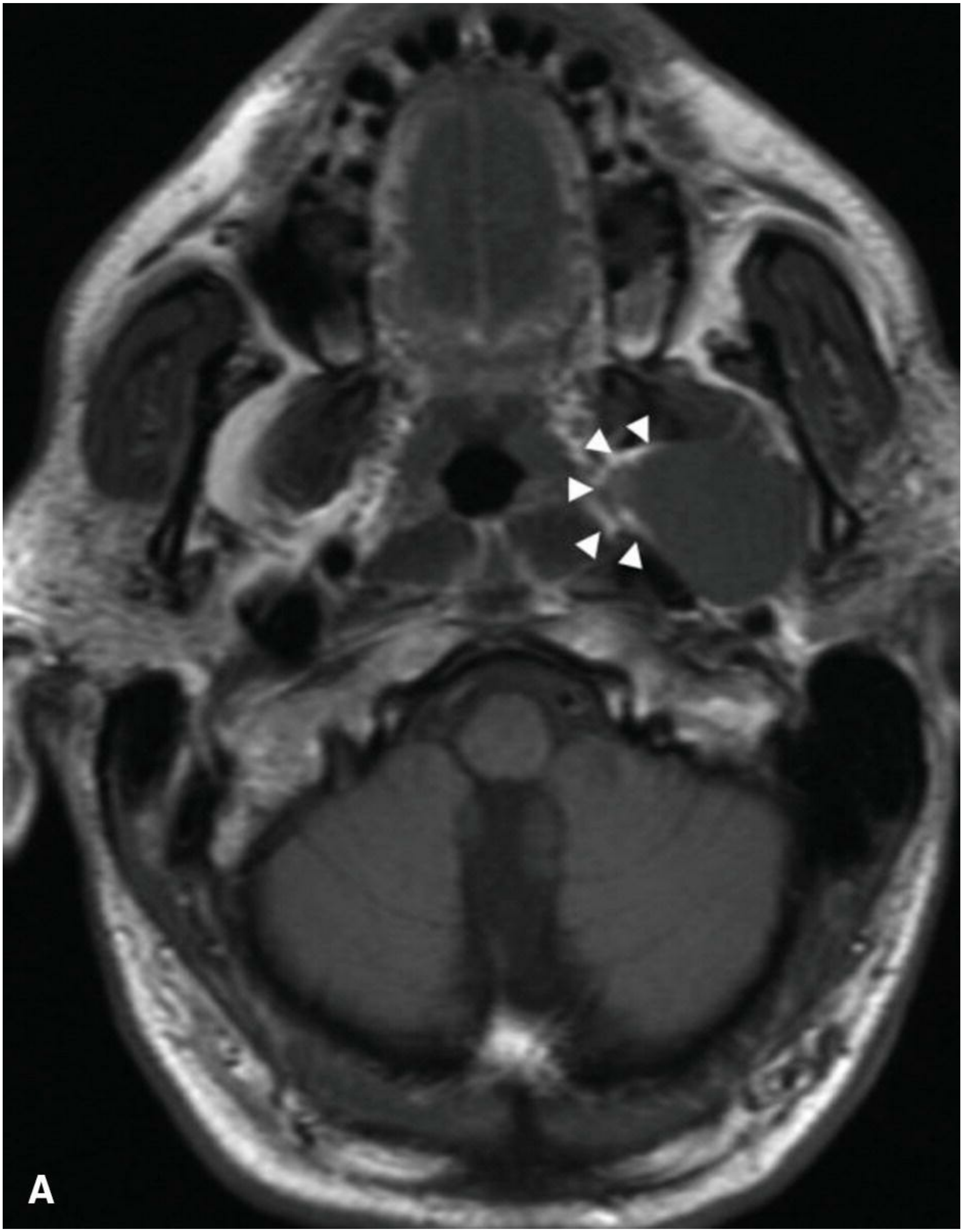
Proper imaging is usually sufficient to determine the type of tumor in the PPS in most cases. Due to this, the use of FNAB for diagnosis is selective. Imaging studies may help differentiate tumors that require surgical resection from those that do not. Also, the extent of operation is infrequently altered by the FNAB results. Nonetheless, FNAB may be used as a diagnostic adjunct for preoperative evaluation of PPS tumors and to aid in treatment planning and patient counseling, in particular if a malignant diagnosis is suspected or in cases of uncertain radiologic interpretation. A number of case series has shown that FNAB confers a diagnostic accuracy of >87% for malignant lesions.[5–8] The overall diagnostic accuracy of FNAB for all tumor types when compared to histopathologic analysis of resected surgical specimens has ranged from 36% to 61%.[5,6,8] A recent study has highlighted a significant improvement in diagnostic accuracy when liquid-based cytology is employed in the place of conventional smear preparations.[5] Coordination of care with a cytopathologist at the time of FNAB can help to ensure a satisfactory specimen quality especially in cystic lesions.

COMMON PARAPHARYNGEAL SPACE TUMORS

Salivary Tumors

Salivary gland tumors within the PPS can arise from the deep lobe of the parotid gland or from ectopic salivary gland tissue within the PPS itself, and they constitute the most common PPS tumors. Distinguishing between these two entities is not possible on physical examination. Radiologically, deep lobe parotid tumors extending into the PPS are observed to be contiguous with the parotid gland, whereas de novo tumors have a clear plane of

separation with the overlying parotid tissue. Consequently, the overlying parotid tissue can be spared in the excision of de novo tumors although this is not often possible for contiguous tumors of the parotid deep lobe. A comprehensive discussion of salivary tumors is covered in Chapter 21. However, here we aim to present the key imaging characteristics of these tumors. Pleomorphic adenomas are the most common tumors arising from the prestyloid PPS.[9–11] There is a degree of heterogeneity observed on CT and MRI, depending on the size of the tumor with more uniform characteristics observed in smaller tumors. On MRI, smaller tumors are usually well circumscribed with a low-intensity T1 signal that enhances homogenously on postcontrast imaging with a hyperintense T2 signal (Fig. 22.3). Larger tumors are often lobulated and may demonstrate areas of hyperintense or hypointense signal intensity attributed to calcification, necrotic, or hemorrhagic areas within the tumor (Fig. 22.4).[12] Malignant degeneration can occur in pleomorphic adenomas giving rise to carcinoma ex pleomorphic adenoma or carcinosarcoma. These malignancies are associated with a high frequency of metastasis to regional lymph nodes and can also metastasize to the lungs, bone, and brain.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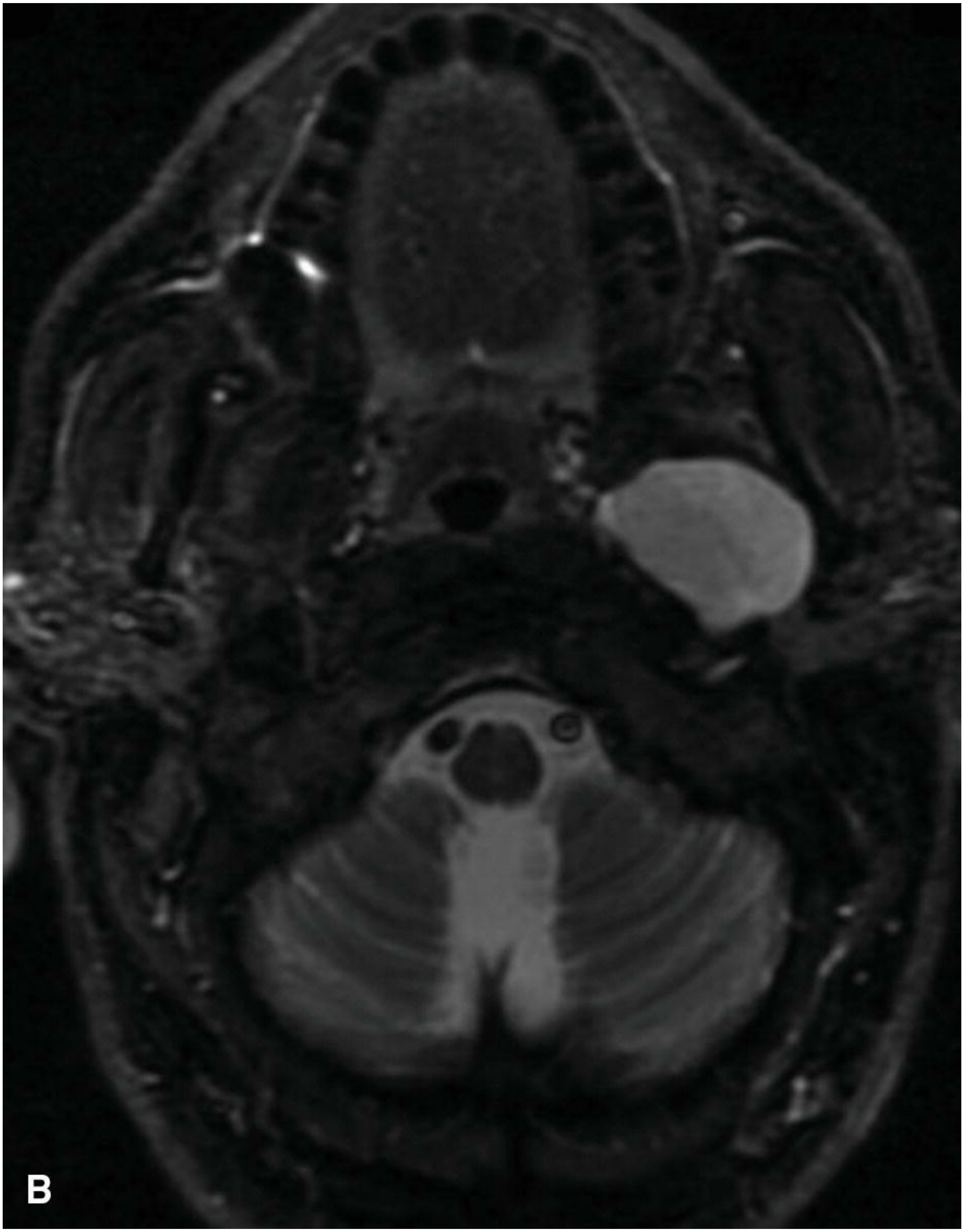


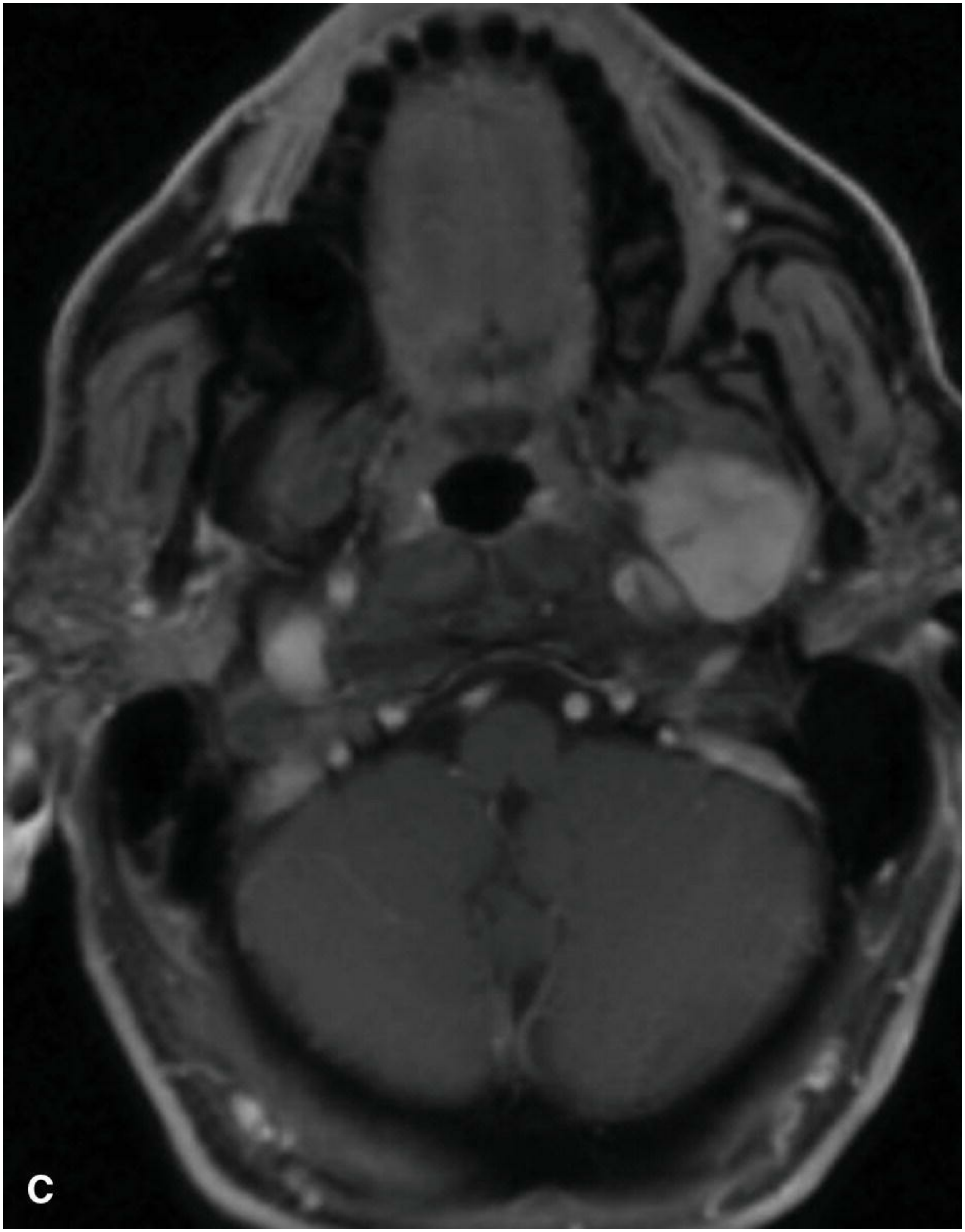
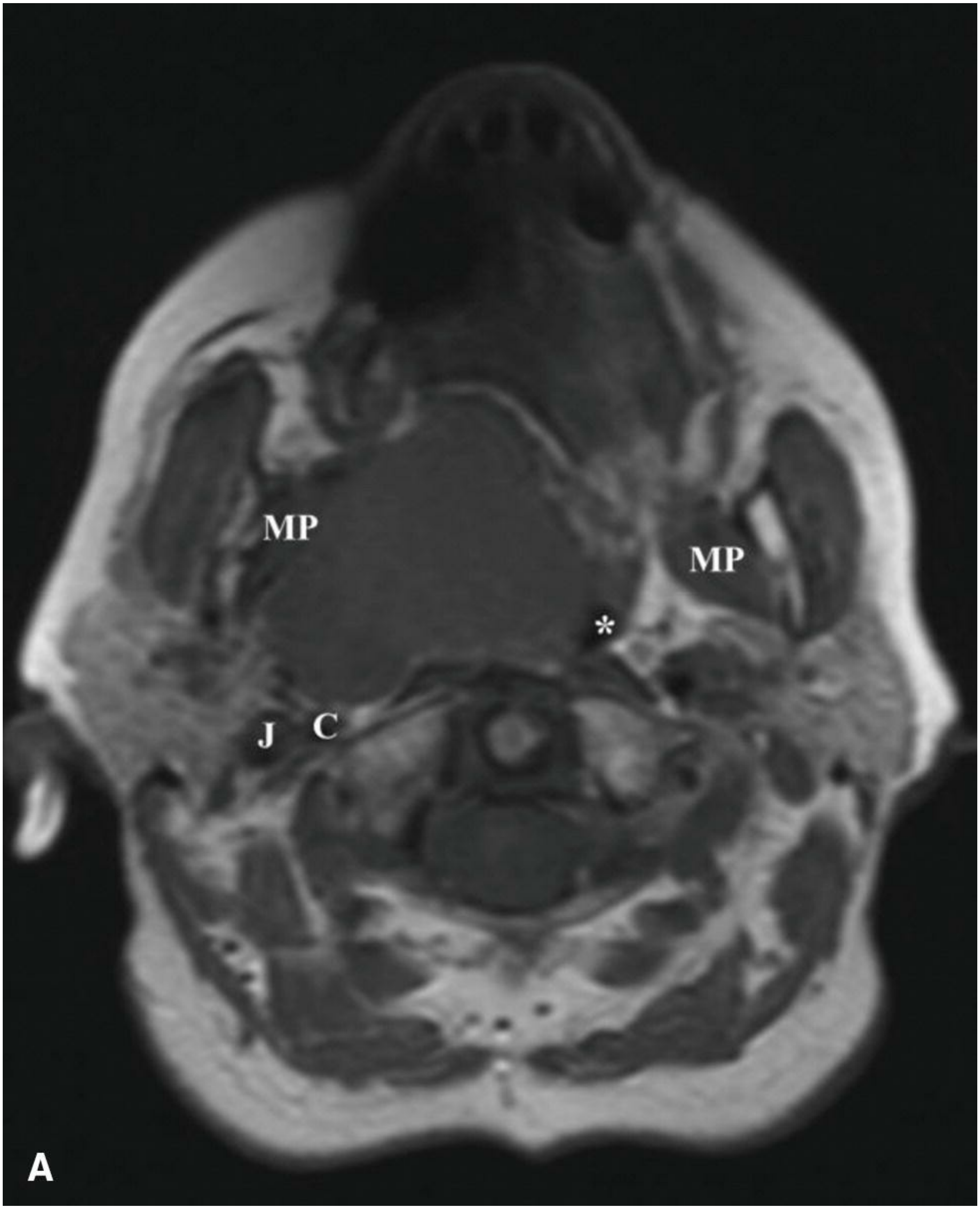


Figure 22.3. Pleomorphic adenoma. T2 hyperintense well-circumscribed homogeneously enhancing mass arises from the prestyloid PPS. Note

anteromedial displacement of the prestyloid parapharyngeal fat (*arrowheads*, high signal intensity on T1-weighted image). The mass homogeneously enhances on postcontrast images. These tumors arise from ectopic salivary gland tissue in the prestyloid PPS or from medial extension of the deep lobe of the parotid gland. **A:** T1-weighted image. **B:** T2 STIR image. **C:** T1-weighted postcontrast image with fat suppression.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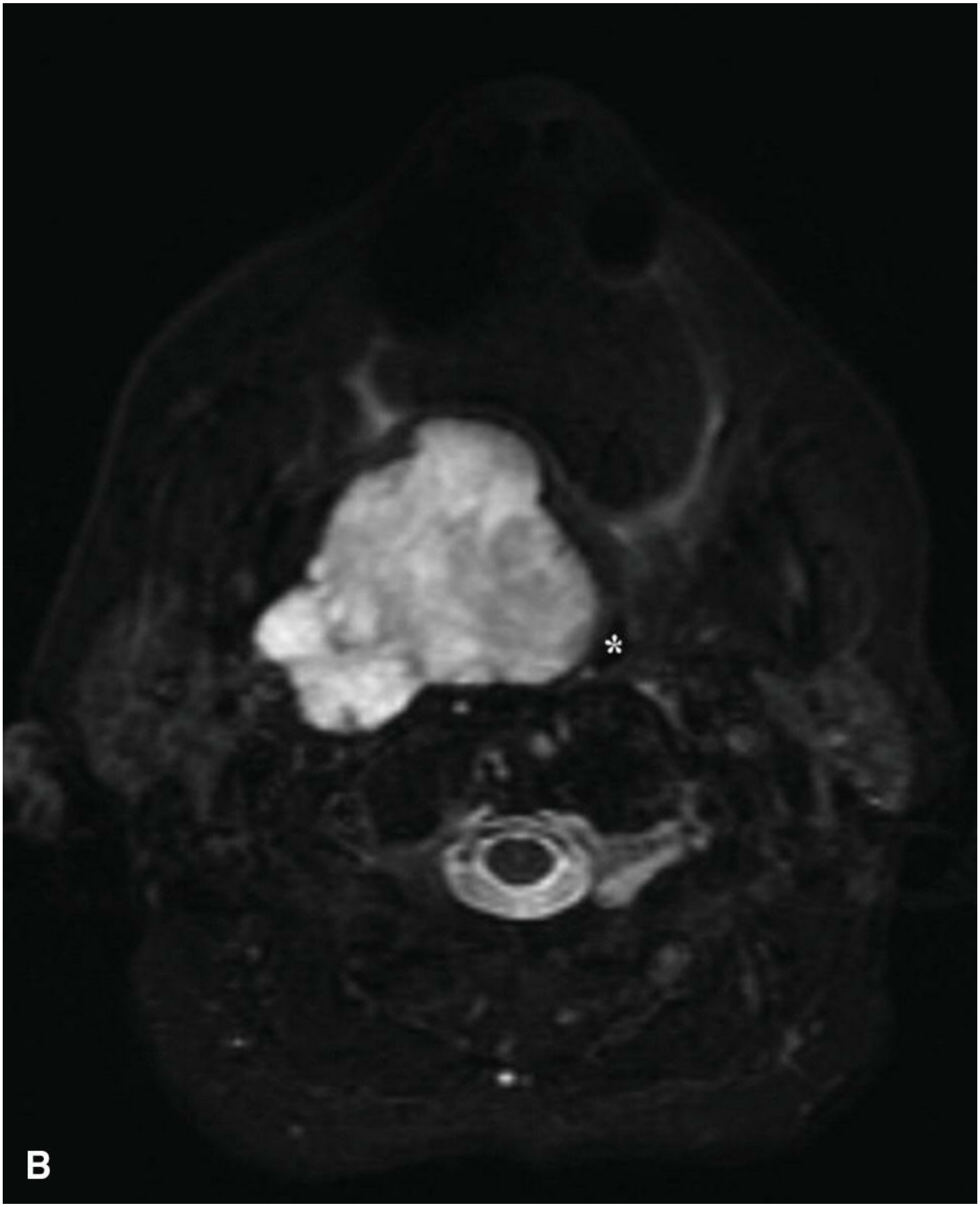
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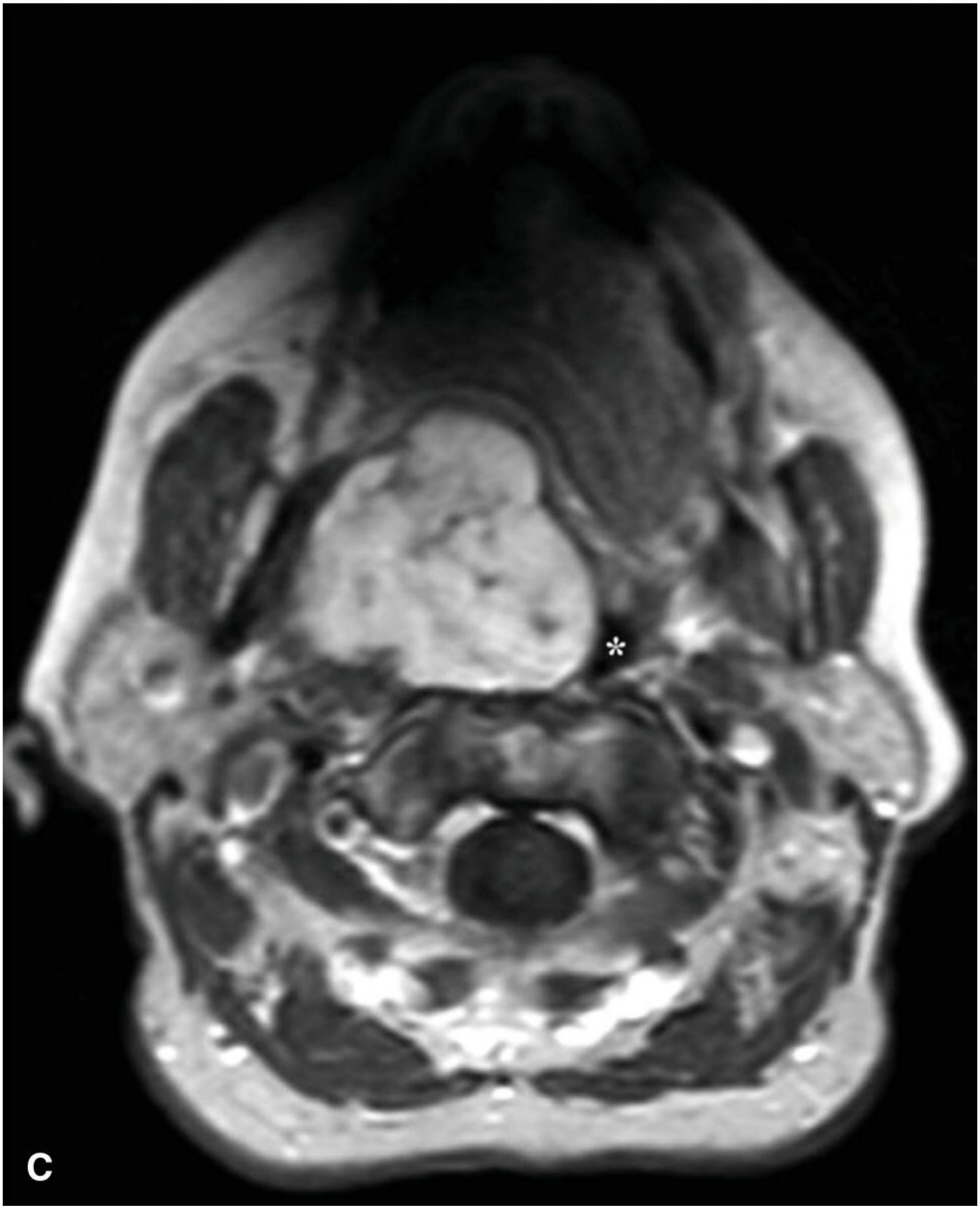
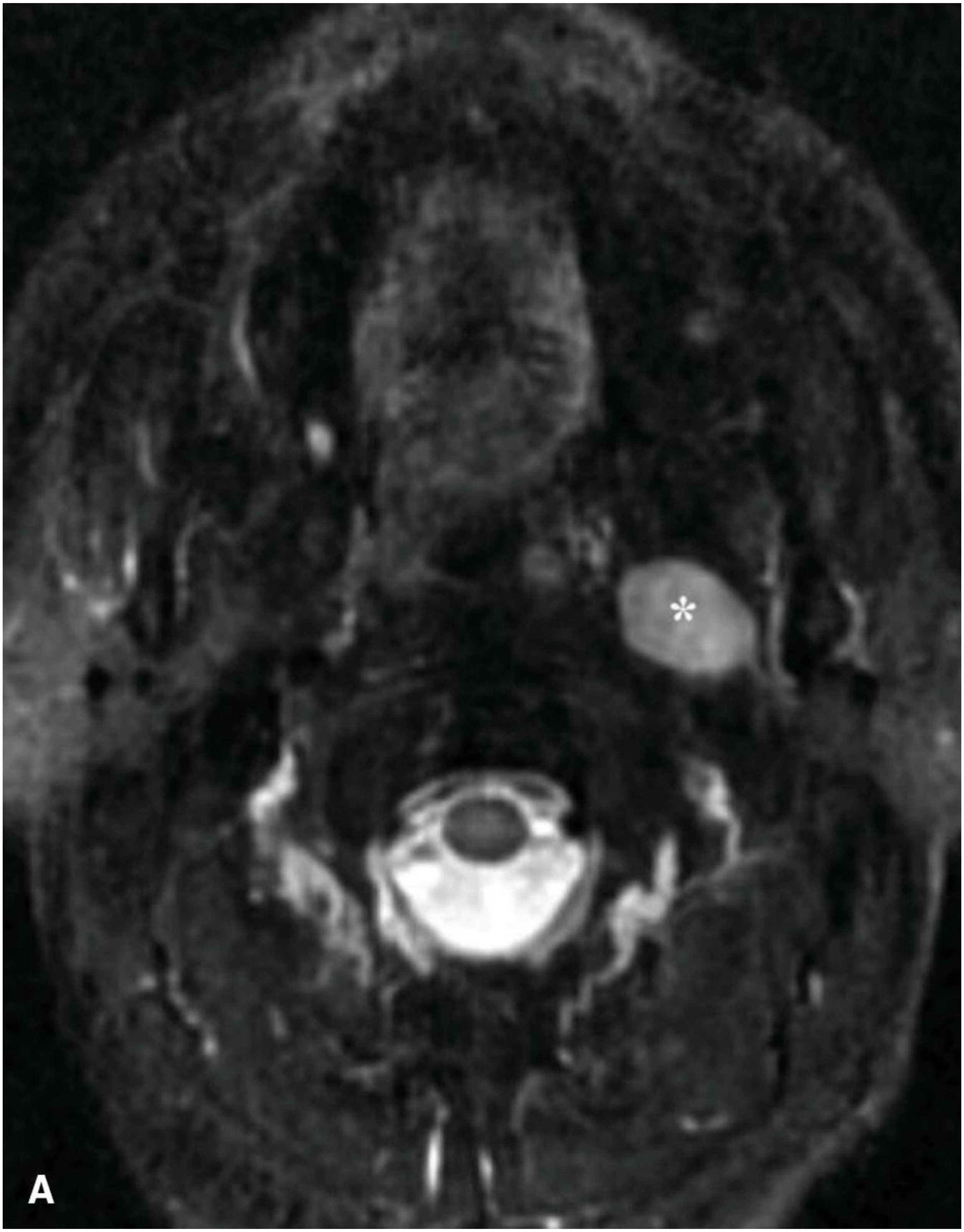


Figure 22.4. Large pleomorphic adenoma in a 77-year-old woman found to have deviation of the uvula on dental examination. Large lobulated mass in the right prestyloid PPS demonstrating heterogeneously intense T2 signal and

avid heterogeneous enhancement with flow voids. Note anterolateral displacement of the medial pterygoid muscle (*MP*) on the right, indicating lack of involvement of the masticator space. The mass abuts the deep right parotid gland. There is mass effect on the base of the right tongue with narrowing of the oropharynx (*asterisk*). (*C*, internal carotid artery; *J*, internal jugular vein.) **A:** T1-weighted image. **B:** T2-weighted STIR image. **C:** T1-weighted postcontrast image.

Mucoepidermoid carcinoma is the most common malignant tumor of the parotid gland, and imaging findings on MRI vary depending on tumor grade. Lower-grade tumors can exhibit similar features to pleomorphic adenoma with low to intermediate signal on T1 images, intermediate to high signal on T2 imaging correlating with the increased mucin-secreting cellular component, and heterogenous enhancement on postcontrast T1 images. High-grade tumors demonstrate low to intermediate signal on both T1 and T2 images with ill-defined margins.

As a general principal, features of salivary gland neoplasms on MRI that have been shown to be indicative of malignancy include low signal intensity on T2-weighted imaging, ill-defined margins on postcontrast images, and perineural involvement. The radiologic features of benign parotid tumors and low-grade malignancies share similarities on MRI, and definitive diagnosis based on imaging studies alone can be a challenging task. The use of dynamic contrast MRI with analysis of peak contrast enhancement and subsequent time frame of contrast washout can assist in distinguishing between Warthin tumor and malignant lesions.[13,14] The comparison of various apparent diffusion coefficient (ADC) of tumors on diffusion-weighted MRI has also been analyzed, with higher ADCs being associated with pleomorphic adenomas and Warthin tumors and lower ADCs associated with malignant tumors (Fig. 22.5).[15,16] The use of fluorodeoxyglucose positron emission tomography (FDG PET) for the diagnosis of salivary gland tumors is limited owing to the nonspecific nature of FDG uptake, with some benign tumors such as Warthin tumor demonstrating intense FDG uptake and other malignant tumors such as adenoid cystic carcinoma showing little FDG avidity.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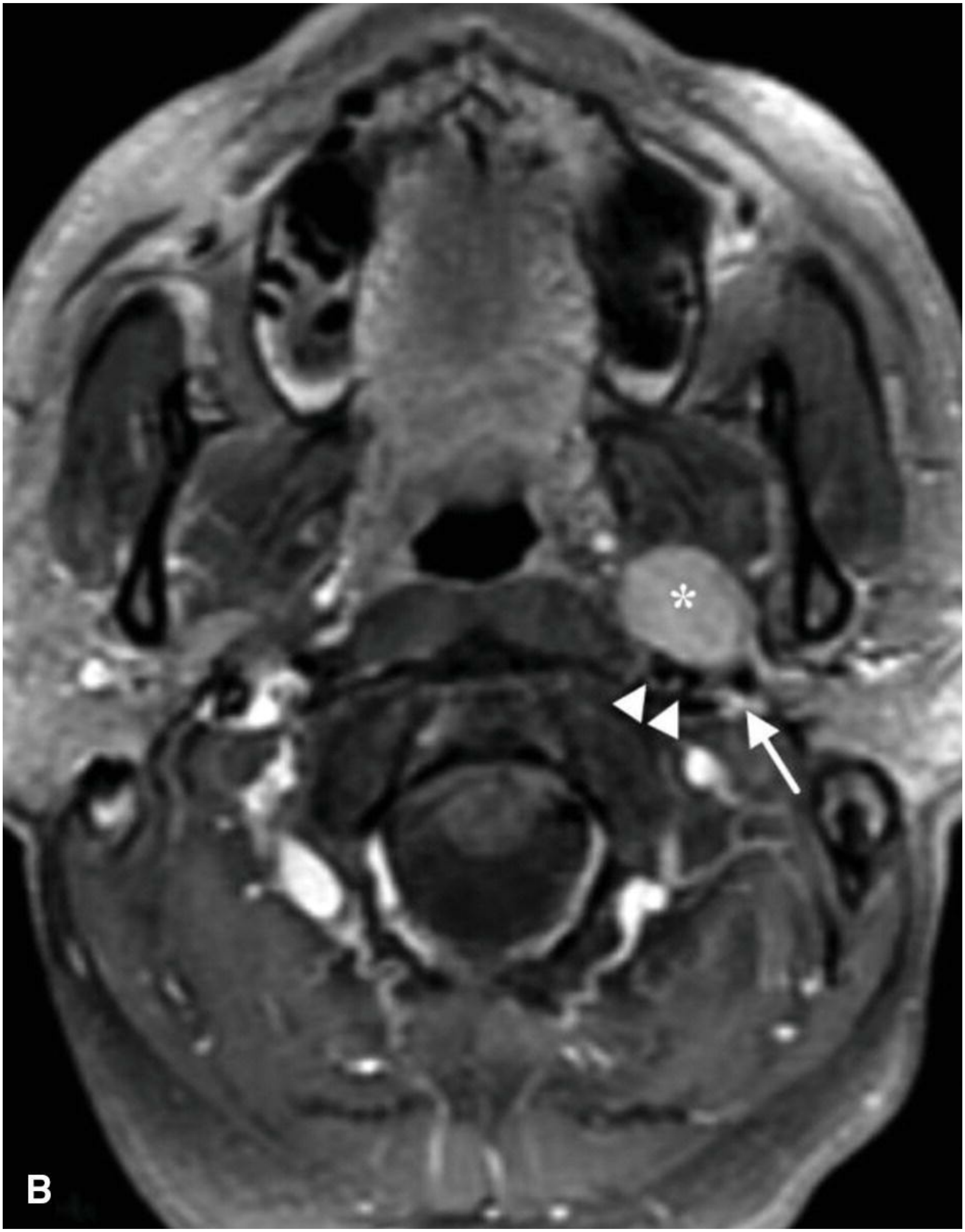
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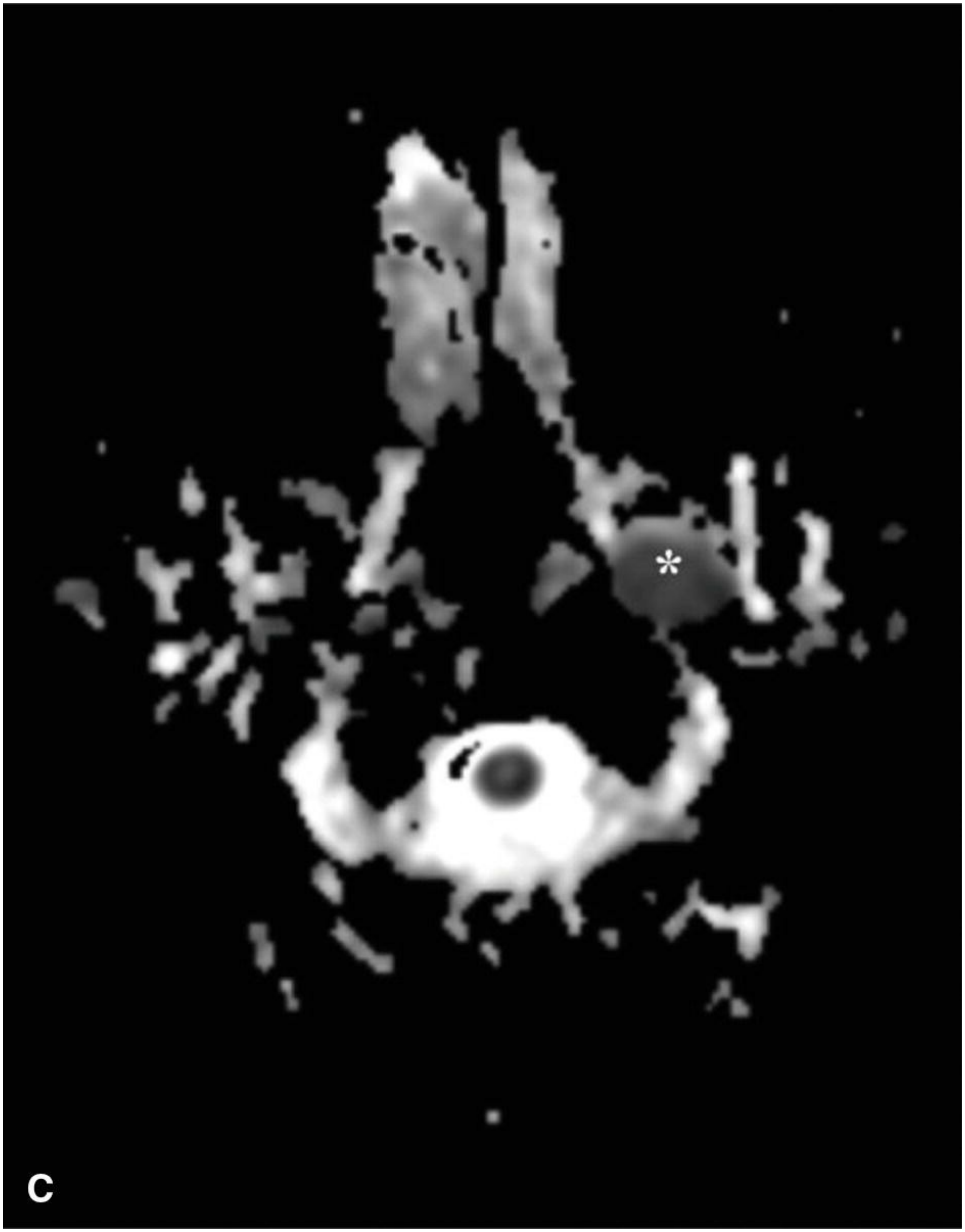
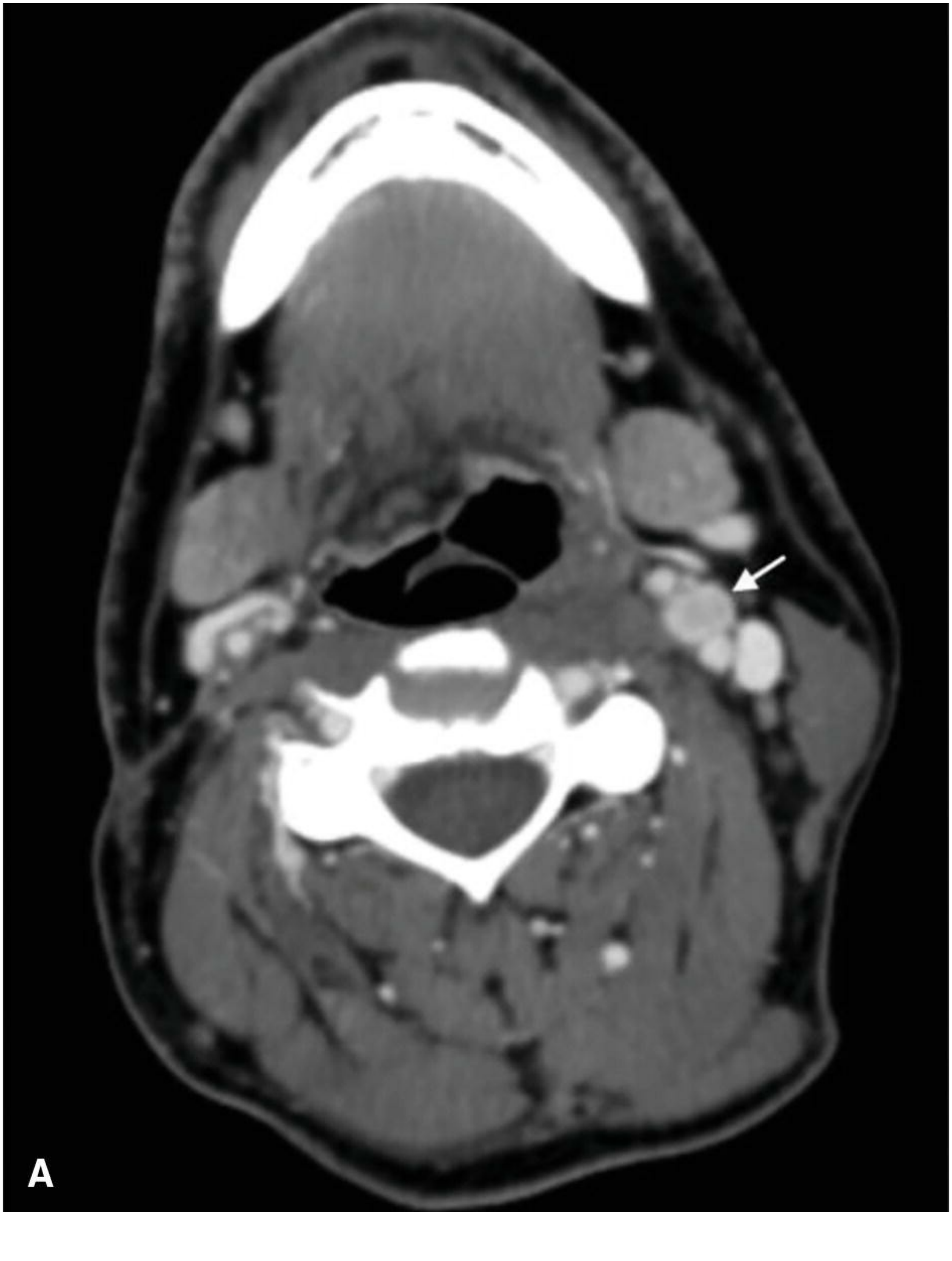


Figure 22.5. Acinic cell carcinoma. Well-circumscribed T2 hyperintense avidly enhancing mass (*asterisk*) in the left prestyloid PPS, anterior to the

carotid arteries (*arrowheads*), and internal jugular vein (*arrow*). In this location, a pleomorphic adenoma is the most common diagnosis; however, it is noted that there is restricted diffusion of the mass (low ADC value), which may be indicative of high cellularity. Pathology demonstrated acinic cell carcinoma. **A:** T2-weighted image. **B:** T1-weighted postcontrast image. **C:** ADC map.

Paraganglioma

Paragangliomas, also known as glomus tumors, are tumors of neural crest origin that have a chemoreceptor function and most commonly arise at the carotid body bifurcation (glomus caroticum), the jugular foramen (glomus jugulare), along the course of the vagus nerve (glomus vagale), and within the middle ear space (glomus tympanicum). In contrast to paragangliomas arising from the lower mediastinum, abdomen, or pelvis, the vast majority of head and neck paragangliomas do not secrete catecholamines. Paragangliomas can rarely occur in association with genetic syndromes such as von Hippel-Lindau syndrome, neurofibromatosis type I, MEN2A, and MEN2B. Nonsyndromic paragangliomas occur more frequently and may be caused by genetic mutations involving the hereditary paraganglioma (PGL) genes that code for the succinate dehydrogenase (SDH) enzyme. Genes that have been identified include SDHD gene 1 (PGL1) on chromosome 11q23, SDHB gene (PGL4) on chromosome 1p35-p36, SDHC gene (PGL3) on chromosome 1q21, and the PGL2 gene, of which the exact location on chromosome 11 remains unknown. PGL3 and PGL4 are inherited in an autosomal dominant form, whereas PGL1 and PGL2 are subject to maternal imprinting. As such, children inheriting the PGL1 and PGL2 genes only express the phenotype if the diseased gene is inherited from the father.[17] SDHD and SDHB mutations show an age-related penetrance showing 86% and 77% penetrance by age 50, respectively.[18] SDHD mutation carriers manifest head and neck paragangliomas and multifocal disease more commonly (Fig. 22.6), whereas SDHB carriers have an increased frequency of malignant paragangliomas in addition to a predisposition toward thyroid cancer and renal cancer.[18,19]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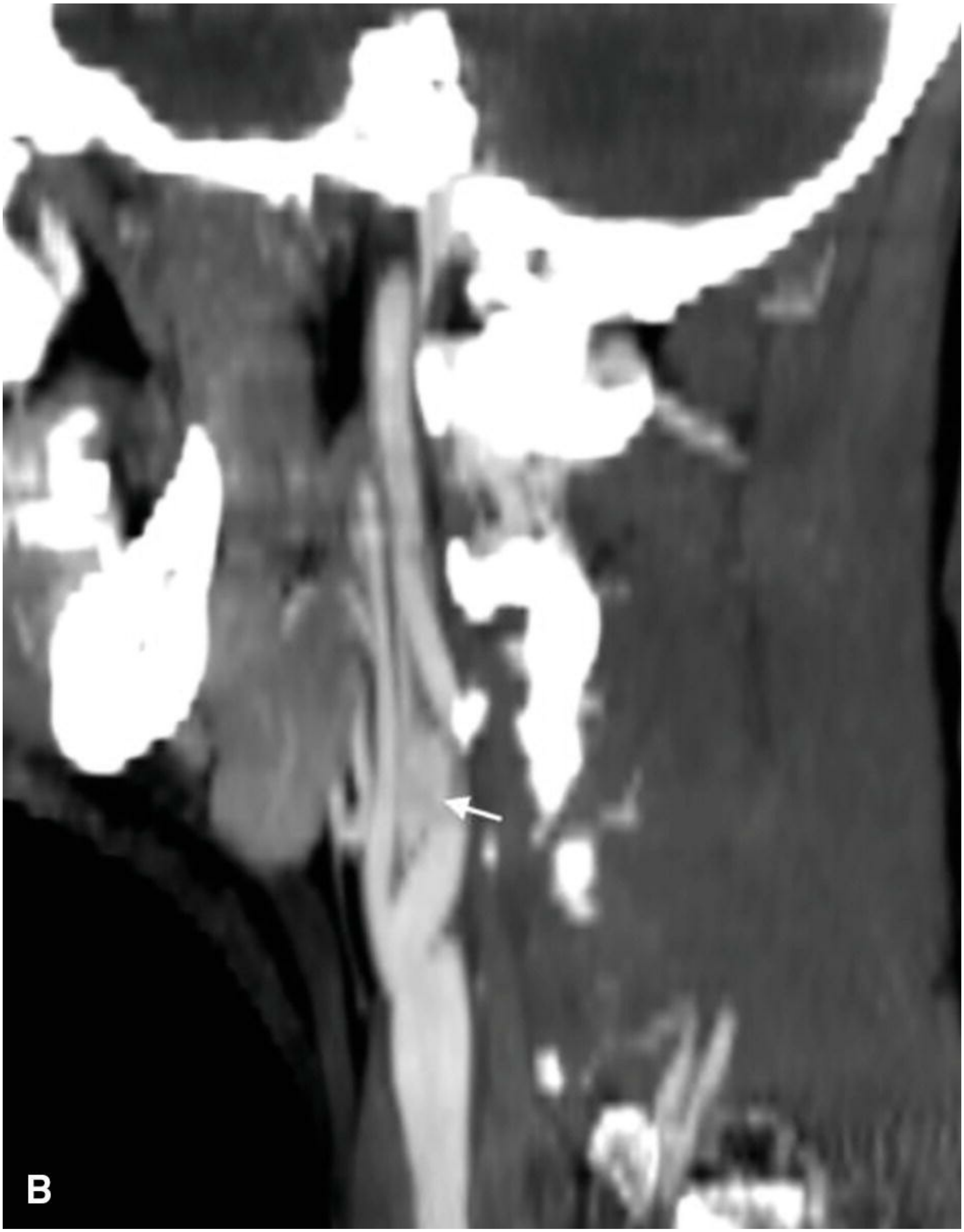
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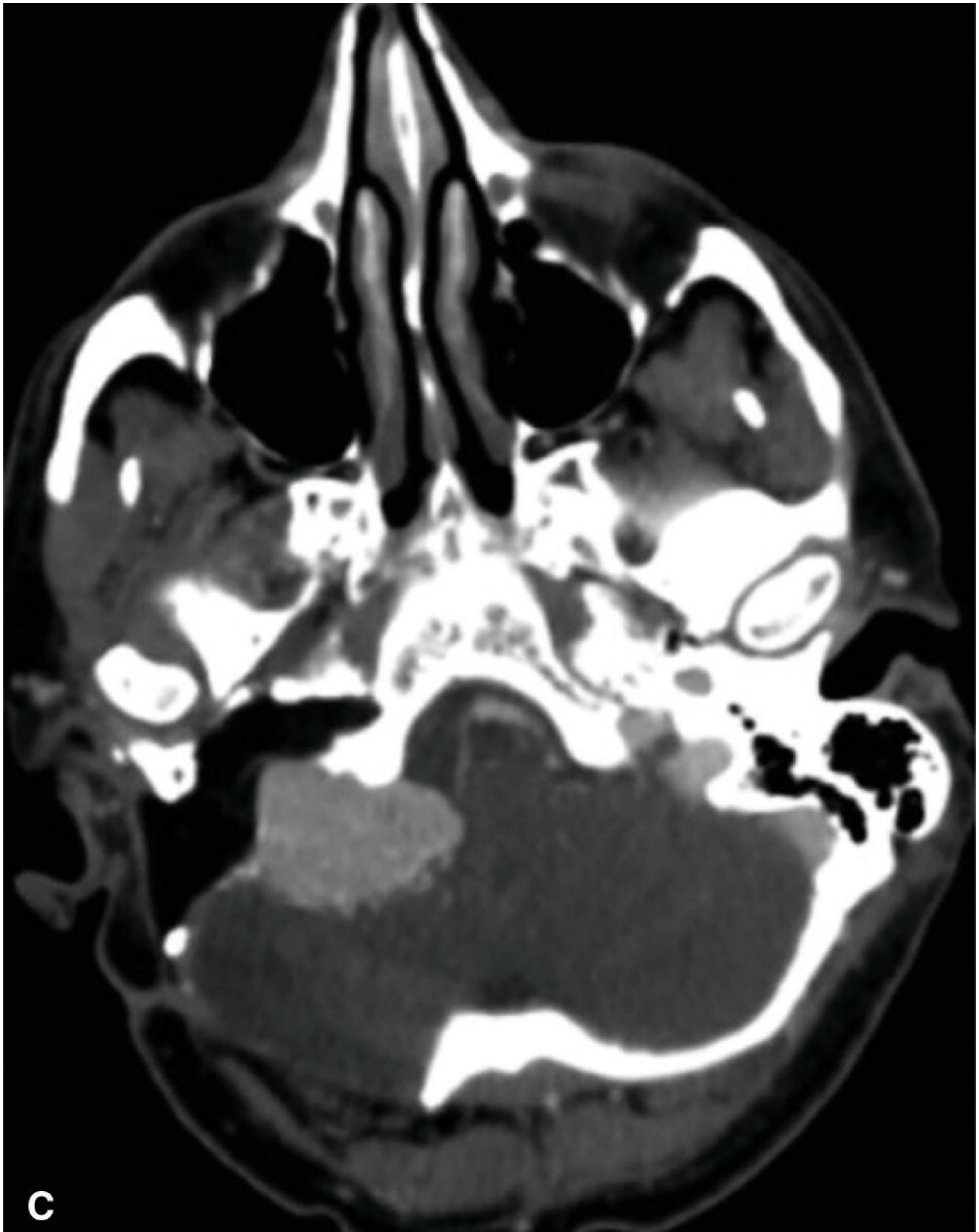
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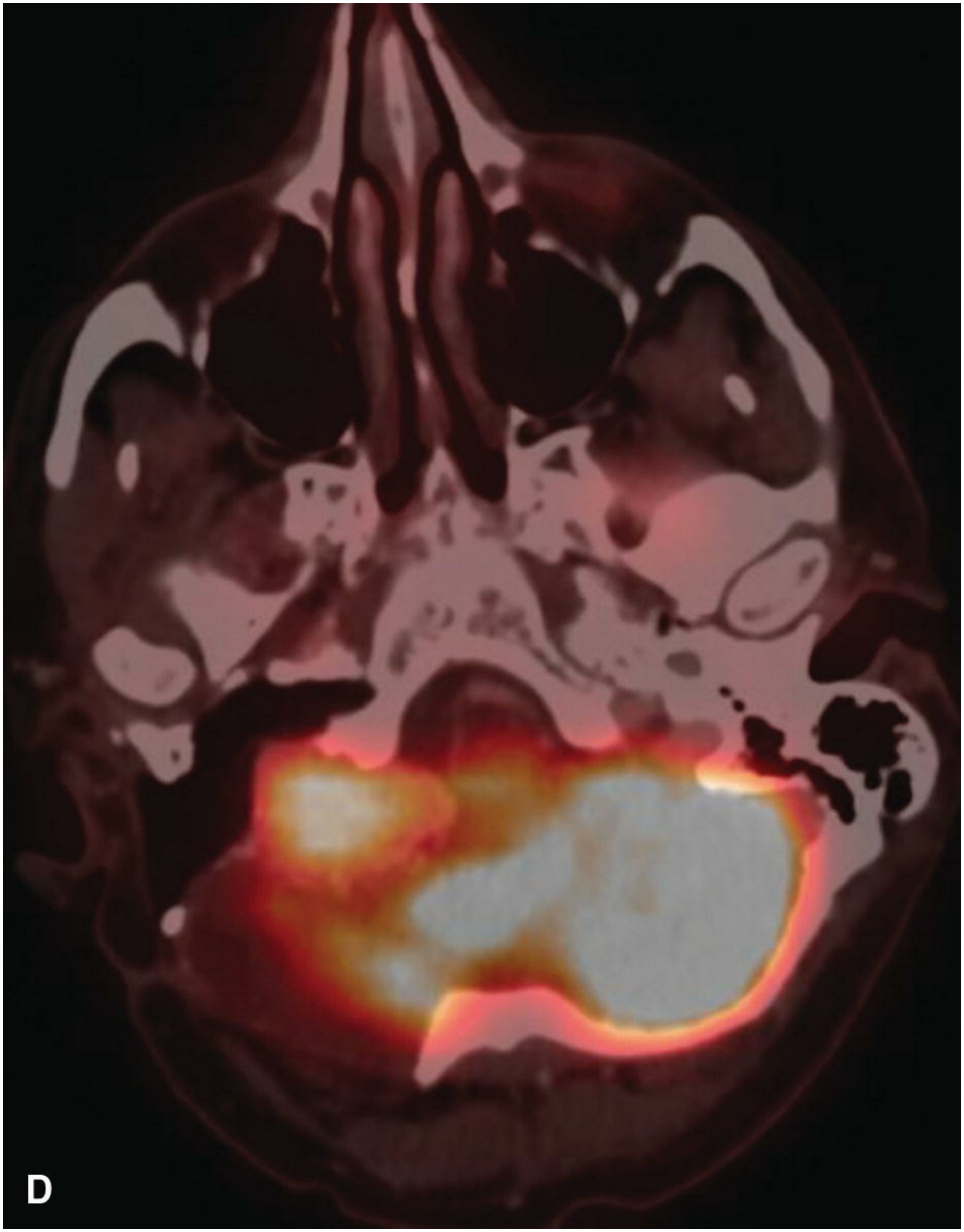


Figure 22.6. Small carotid body tumor (Shamblin type I). Thirty-nine-year-old man with history of succinyl dehydrogenase D mutation and multiple

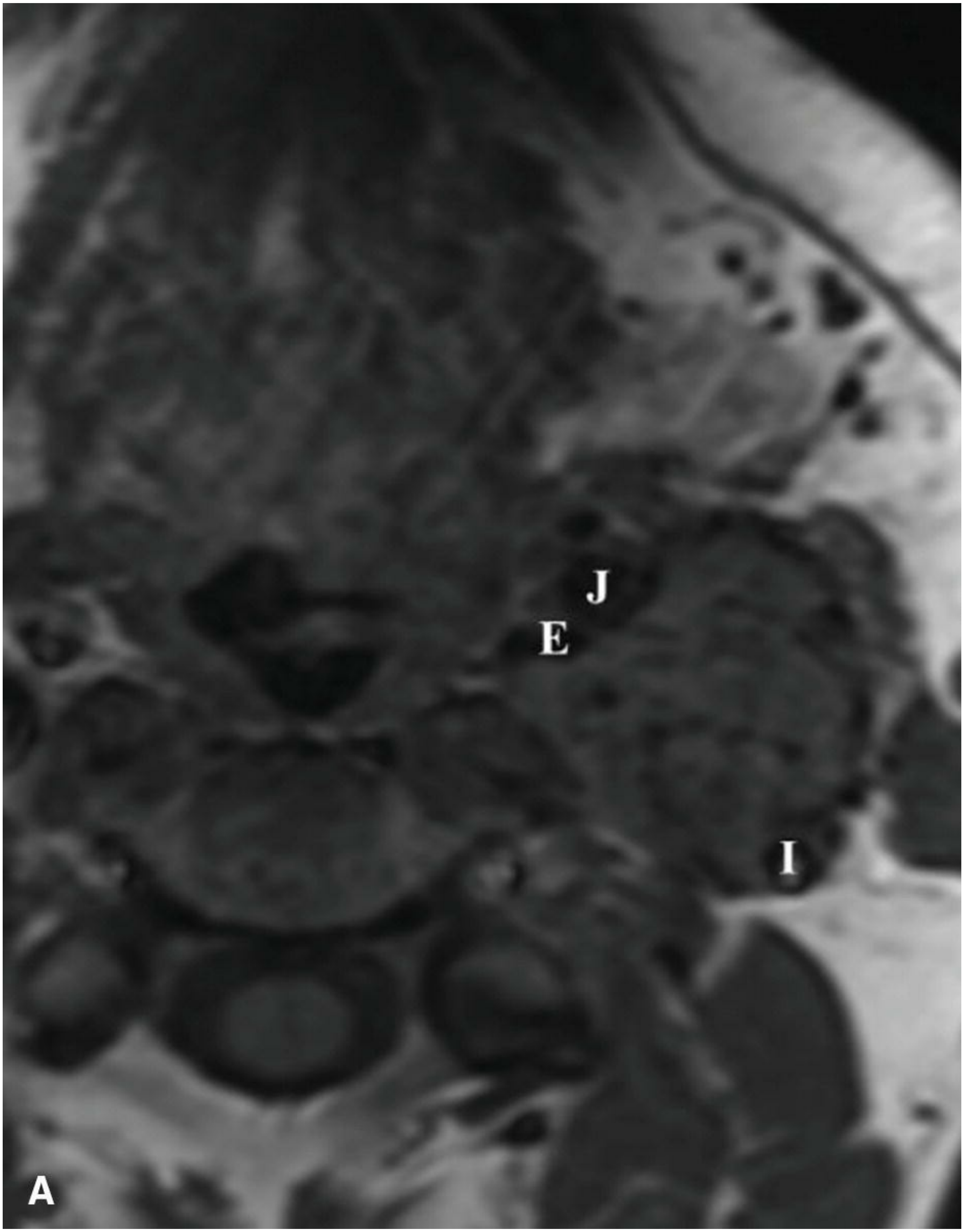
paragangliomas. Axial **(A)** and sagittal **(B)** contrast-enhanced CT images demonstrate small enhancing mass (*arrows*) at the left carotid bifurcation with mild splaying of the internal and external carotid arteries. This patient also has large enhancing mass extending from the right jugular foramen at the cerebellopontine angle (glomus jugulare tumor) with prior right occipital and petrous temporal decompressive surgery **(C)**. Both lesions were intensely FDG avid on PET–CT **(D)**.

Screening for SDH mutations should be carried out in family members of patients with a clinical history of familial paraganglioma, those with an age of presentation below 45 years, and those with multiple synchronous or metachronous tumors. SDHB mutation testing should be considered in all patients with a malignant tumor. In individuals known to have familial paraganglioma, genetic testing should commence at age 10 or at least 10 years before the earliest age of diagnosis in relatives affected. Periodic clinical, biochemical, and imaging surveillance has been recommended to include 24-hour urinary excretion of fractionated metanephrines and catecholamines and MRI or CT scan imaging of the skull base every 2 years and MRI or CT imaging of the thorax, abdomen, and pelvis every 4 years.[20] Meta-iodinated benzylguanidine (MIBG) scintigraphy has traditionally been used to detect paragangliomas or metastatic disease not visualized on CT scan or MRI with sensitivities between 77% and 90% and specificity between 88% and 96%, with the addition of SPECT improving sensitivities to between 88% and 96%.[21] Over the past decade, there has been an increasing interest in the use of positron emission tomography (PET) as an alternative to MIBG scintigraphy, with PET imaging shown to have a higher sensitivity in detecting distant metastasis in patients with SDHB mutations.[22,23]

Histologically, paragangliomas consist of two different cell types organized into clusters separated by a fibrovascular stroma pathognomonically known as Zellballen (“cell balls” in German). Type I cells, also known as chief cells, have a polygonal shape and eosinophilic cytoplasm and are concentrated in the center. Type II, or sustentacular cells, are spindle shaped and surround the periphery of the Zellballen. Rarely, paragangliomas can secrete catecholamines and may present with headaches, palpitation, tremor, and profuse sweating. Patients with these symptoms should be tested for 24-hour urinary collection of metanephrine,

normetanephrine, and vanillylmandelic acid (VMA) and plasma free metanephrines.

These tumors have a lobulated, ovoid appearance on MRI with well-defined margins. On T1 sequences they have signal intensity similar to that of muscle, whereas on T2 sequences they are mildly hyperintense. They enhance rapidly and intensely with gadolinium contrast and larger tumors possess punctuate areas of flow voids, which may confer the classic “salt-and-pepper” appearance (Figs. 22.7 and 22.8). Surgical biopsy of these lesions should be avoided, as they are highly vascular. A mass splaying the internal and external carotid arteries at the bifurcation (i.e., lyre sign) is highly suggestive of a carotid body tumor.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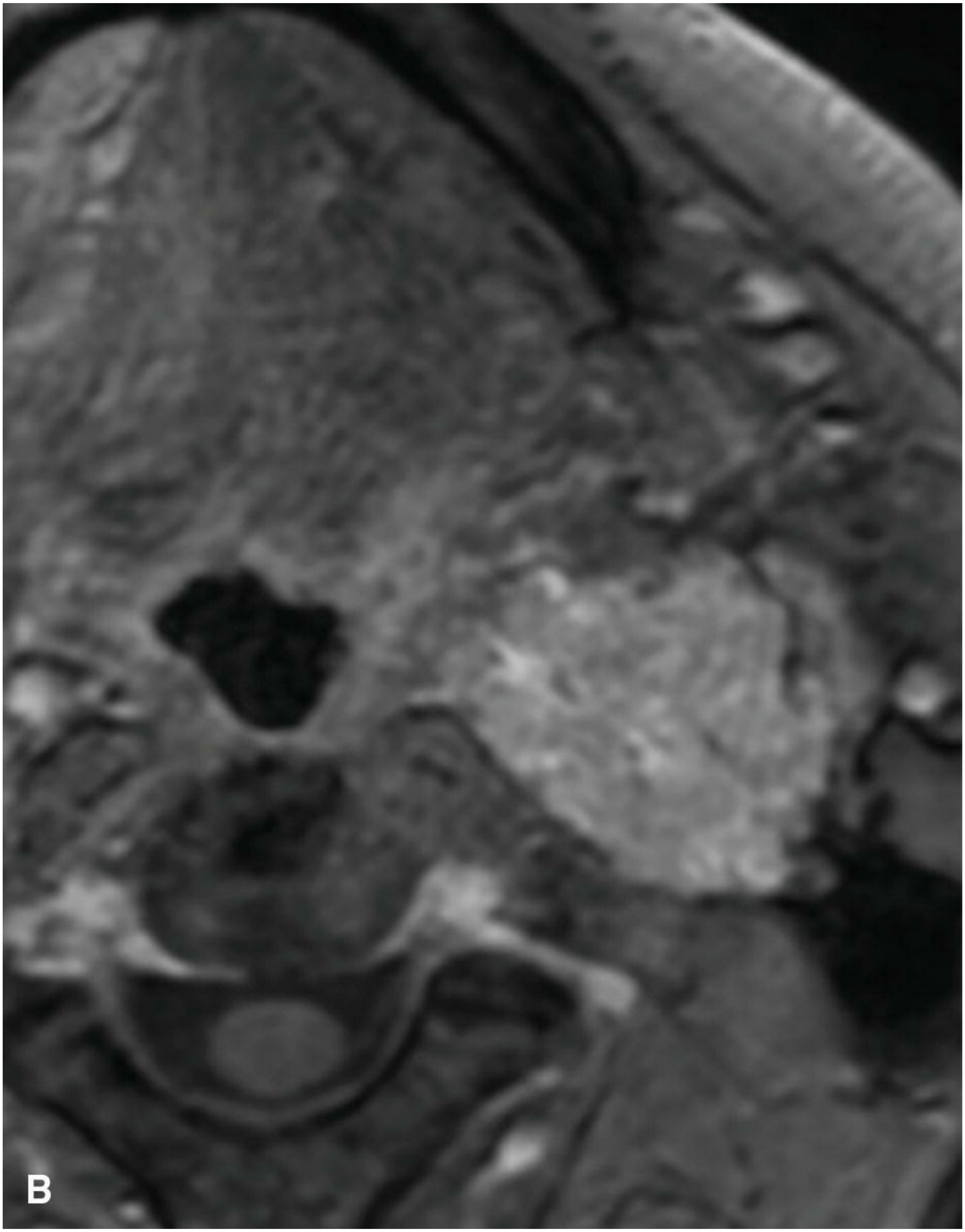
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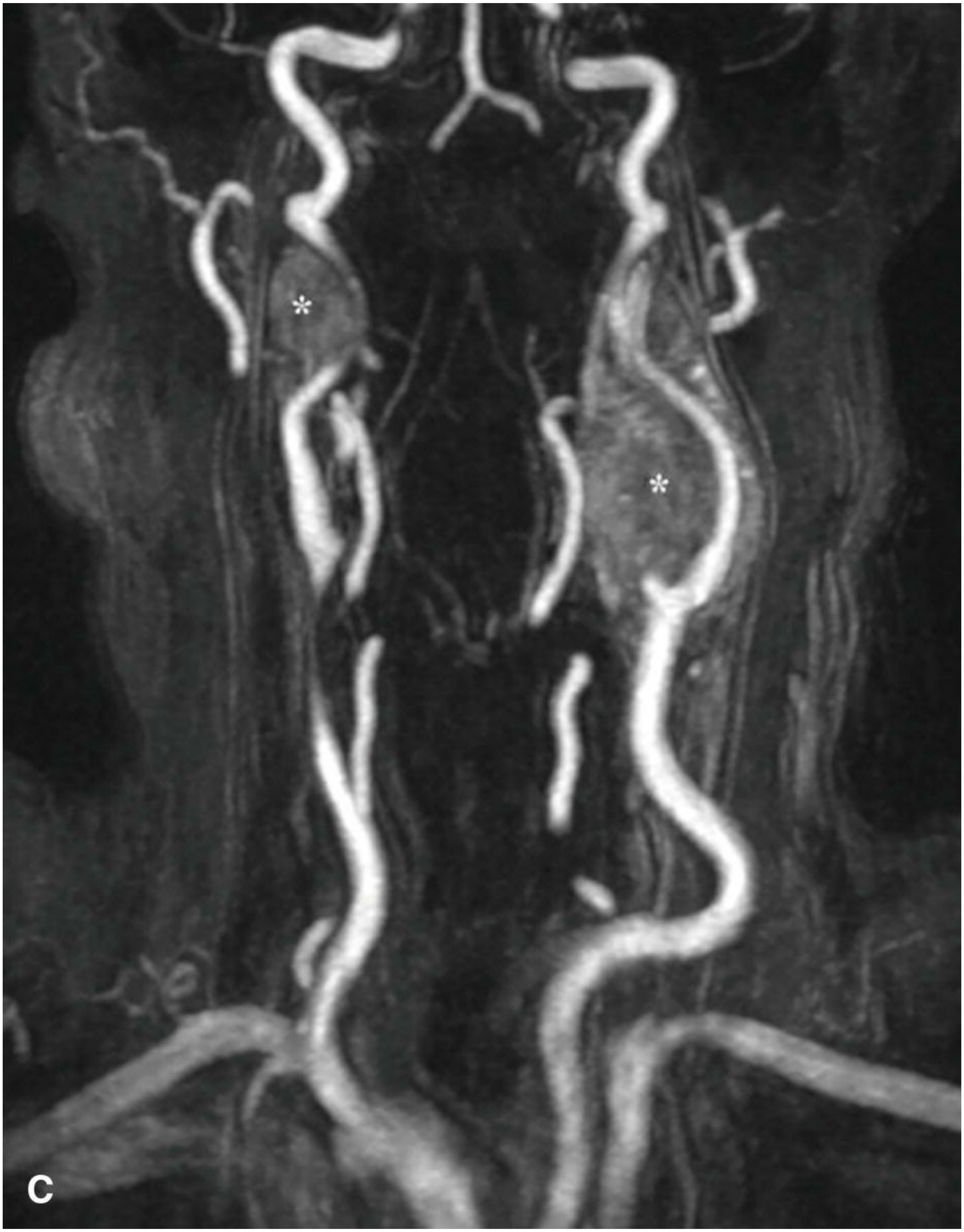
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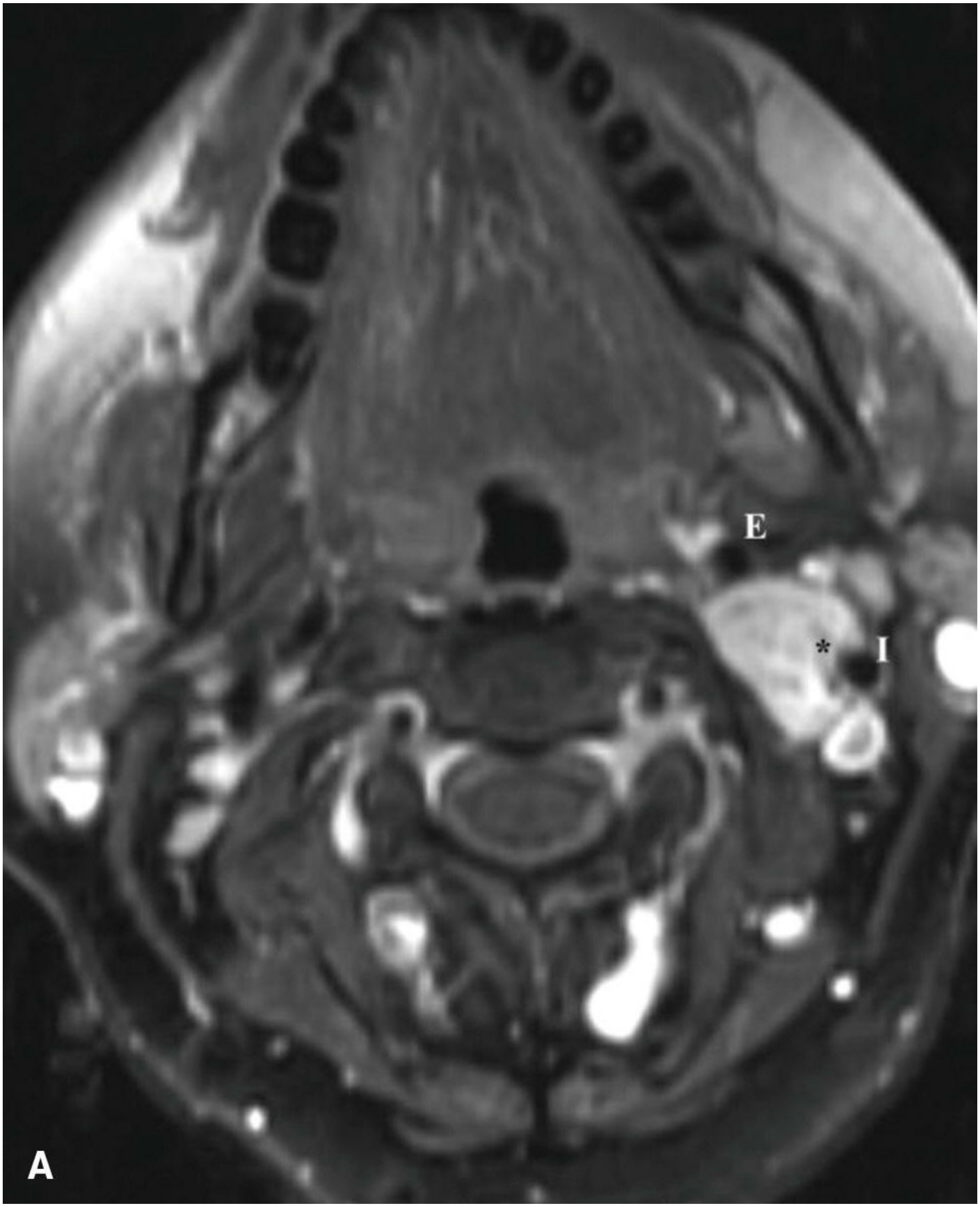
Figure 22.7. "Salt-and-pepper" appearance of paraganglioma. Fifty-nine-year-old man presenting with fullness in the left neck. T1-weighted image

(A) demonstrates “salt-and-pepper” appearance of mass splaying the internal (*I*), external (*E*) carotid arteries and (*J*) internal jugular vein. Low-intensity foci (“pepper”) indicate flow voids due to tumor vascularity (also seen on postcontrast image, **(B)**). High-intensity foci (“salt”) may represent areas of slow flow or hemorrhage. Thin **(C)** and thick **(D)** section multiplanar reformations of MR angiography in this patient demonstrate the carotid body tumor splaying the carotid vessels on the left as well as an additional paraganglioma just lateral to the right internal carotid artery (*asterisks*).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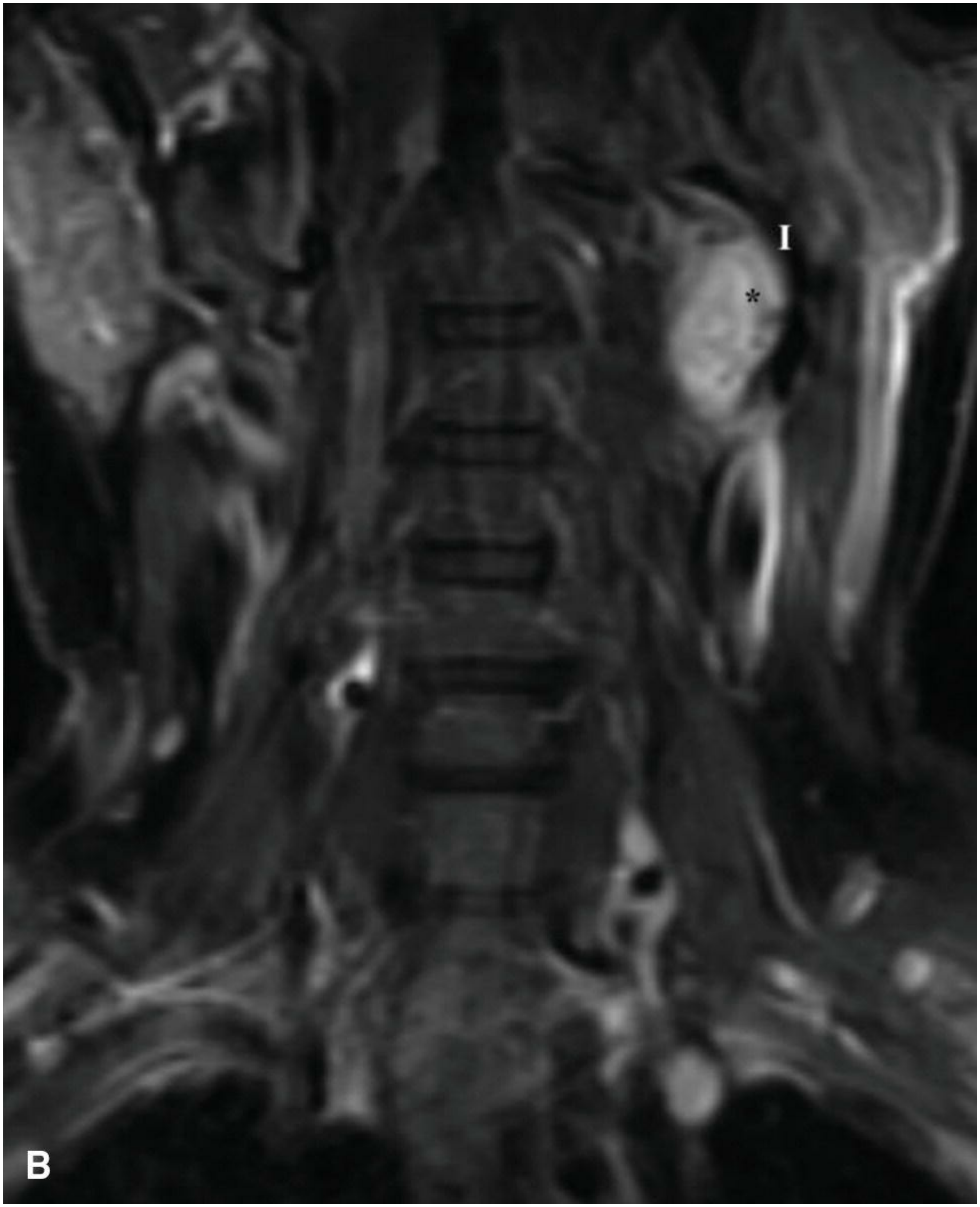
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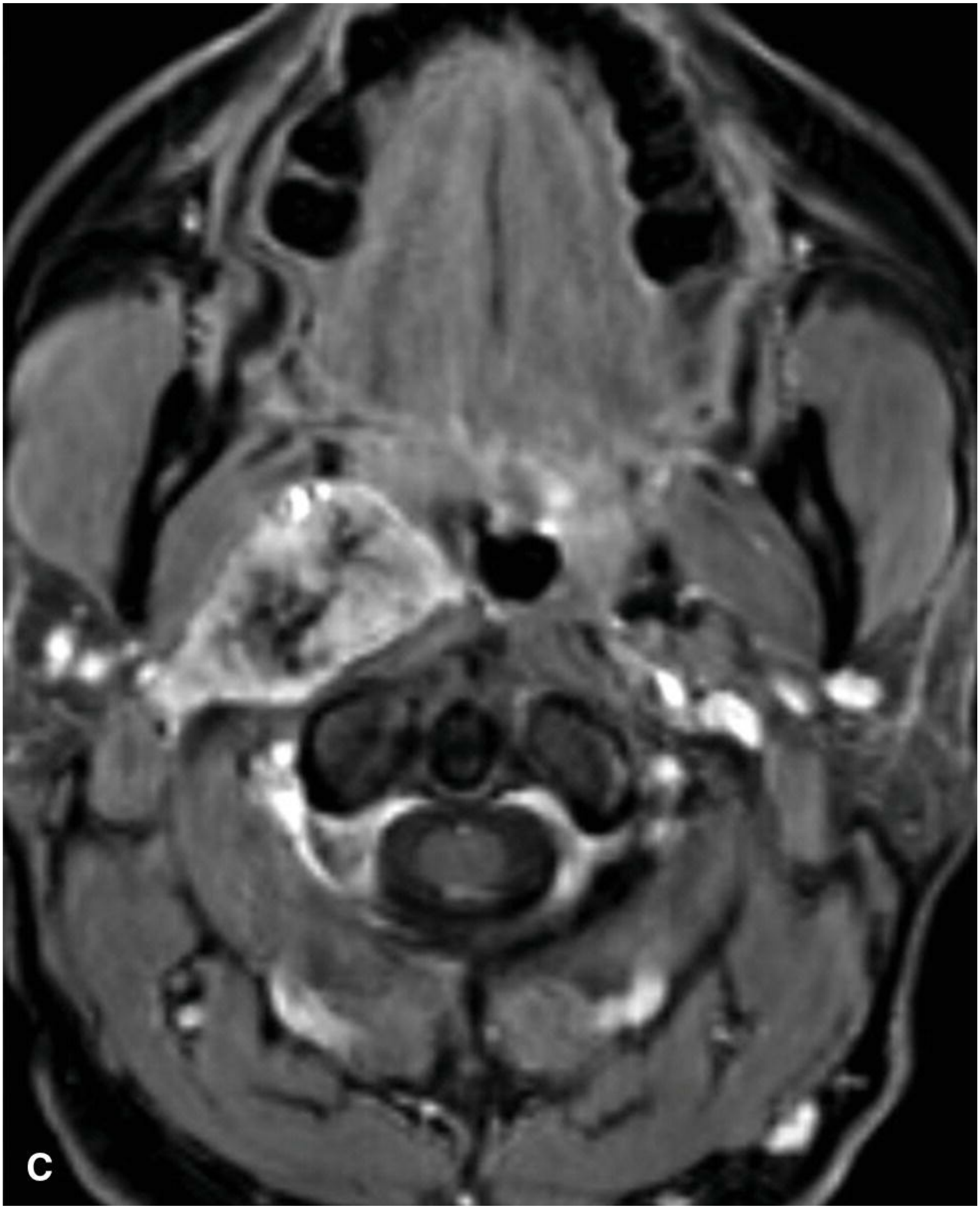


Figure 22.8. Flow voids on MR imaging. A 60-year-old woman presenting with a mass in the neck. **A and B:** T1-weighted postcontrast images demonstrate splaying of the internal (*I*) and external (*E*) carotid arteries by an avidly enhancing mass at the bifurcation, typical of carotid body tumors.

Serpiginous flow voids indicating tumor vascularity can be seen (*black asterisk*). **C:** Another patient with a paraganglioma demonstrating prominent flow voids on postcontrast T1-weighted MRI. Presence of flow voids differentiates paraganglioma from schwannoma.

Shamblin's classification of carotid body tumors based on their relationship to the internal carotid artery (ICA) has recently been correlated with MR imaging. In type I tumors, the area of contact with the ICA is ≤180 degrees, type II tumors contact the ICA 180 to 270 degrees, and type III tumors have an area of contact >270 degrees.[24] Larger type II or type III tumors have been shown to have an increased rate of intraoperative ICA sacrifice, and preoperative balloon occlusion testing is therefore recommended to assess the integrity of collateral circulation to the brain and plan for possible carotid artery replacement preoperatively. In retrospective reviews of patients who experienced intraoperative ICA disruption without undergoing balloon occlusion testing, it is shown that 26% suffered a stroke with a subsequent mortality rate of 12%, compared to a 4.7% stroke rate alone with no mortalities for patients who passed a total balloon occlusion test.[25,26] A wide variety of methods incorporating CT imaging and MRI of cerebral blood flow during balloon occlusion testing and interpretation criteria have been used to assess the adequacy of cerebral blood flow during balloon occlusion testing. No one technique has been demonstrated as being superior in predicting the incidence of permanent neurologic deficit following ICA sacrifice.

Vagal Paraganglioma

The most common origin of paragangliomas of the PPS is from the vagus nerve (Fig. 22.9). Vagal paragangliomas are more closely adherent to the nerve compared to schwannomas, such that at the time of presentation between 20% and 50% of patients have vagal nerve functional deficits.[27] Surgical separation of the tumor from the vagus nerve is not usually feasible, and surgery reliably leads to a complete vagal nerve palsy. Therefore, consideration should be given to serial imaging and observation of tumors with minimal or no growth. In the presence of bilateral vagal paragangliomas or preexisting contralateral vagal nerve palsy, radiation therapy should be considered as an alternative to surgical resection in order to avoid the

morbidity of bilateral vagus nerve deficits.

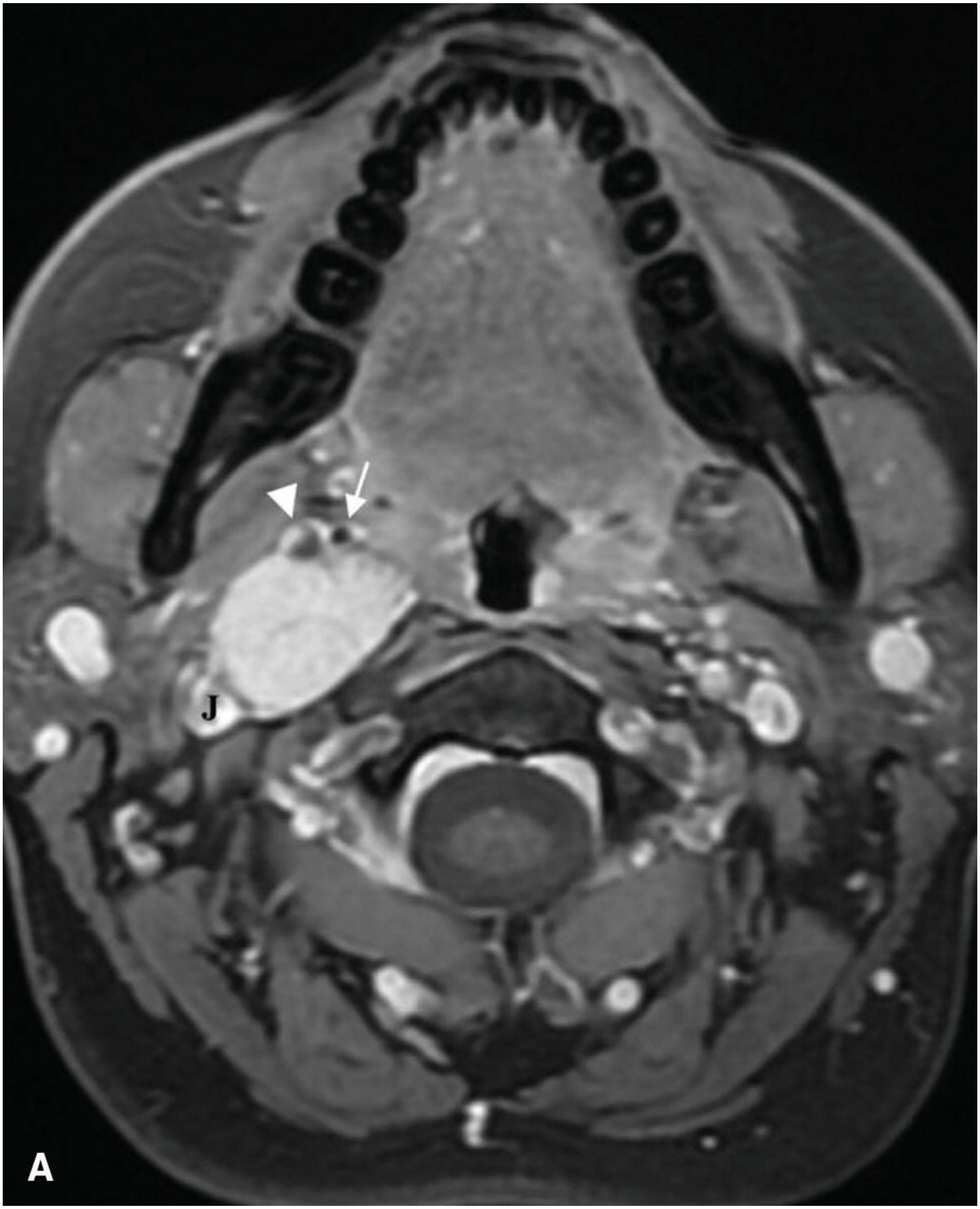
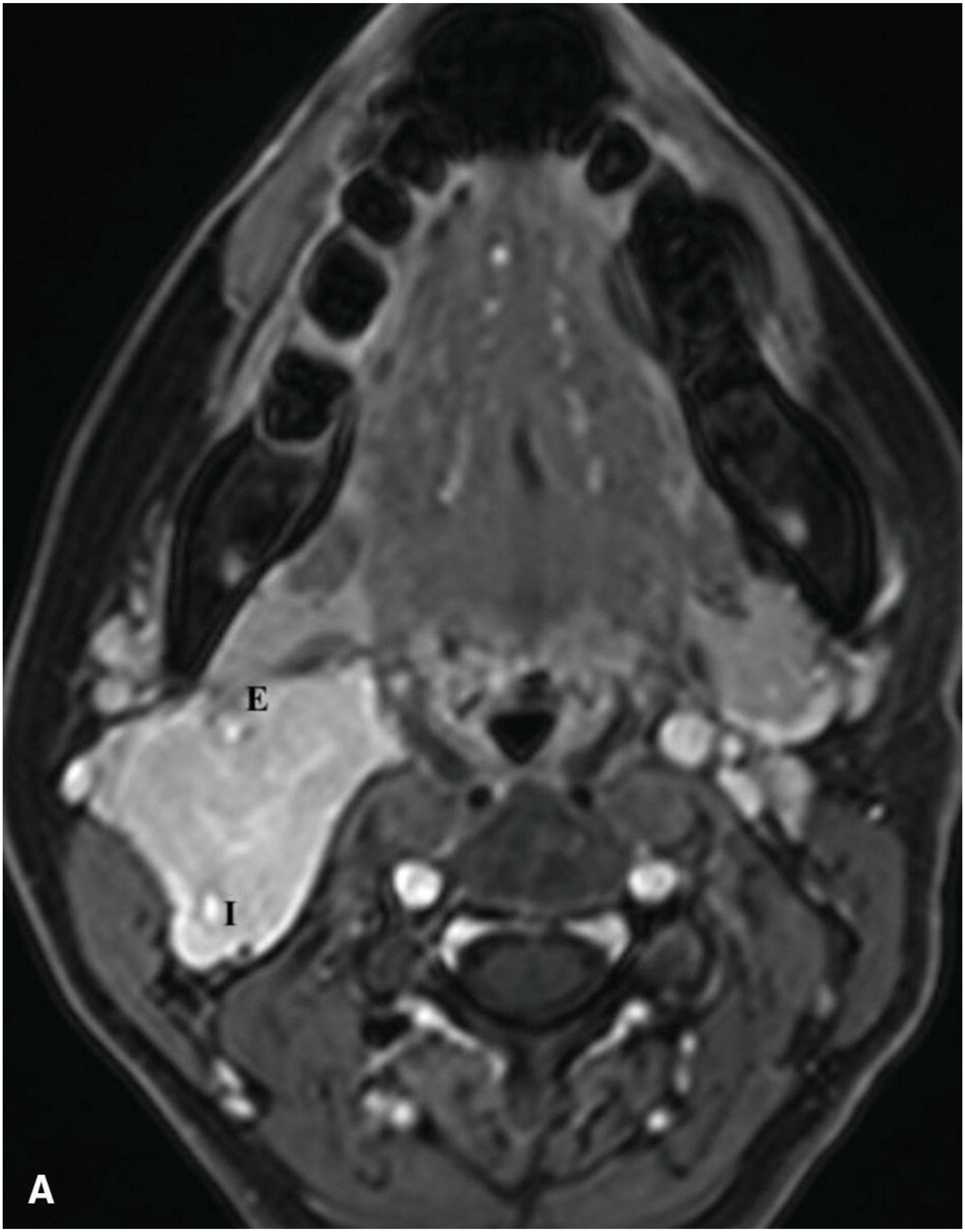


Figure 22.9. Vagal paraganglioma. T1-weighted postcontrast axial **(A)** and sagittal **(B)** images demonstrate a avidly enhancing lesion in the carotid space displacing the internal carotid artery (*arrowheads*) anteriorly away from the

internal jugular vein (*J*). Displacement of both internal and external carotid arteries (*arrow*) anteriorly suggests vagal paraganglioma over carotid body tumor.

Carotid Body Tumors

Carotid body tumors are the most commonly encountered paraganglioma in the lower neck. A large carotid body tumor can extend superiorly into the PPS (Fig. 22.10). On physical examination, these tumors manifest as a mass in the neck that on palpation responds to manipulation in the lateral plane, but not in a cephalocaudad direction as they are tethered to the carotid artery.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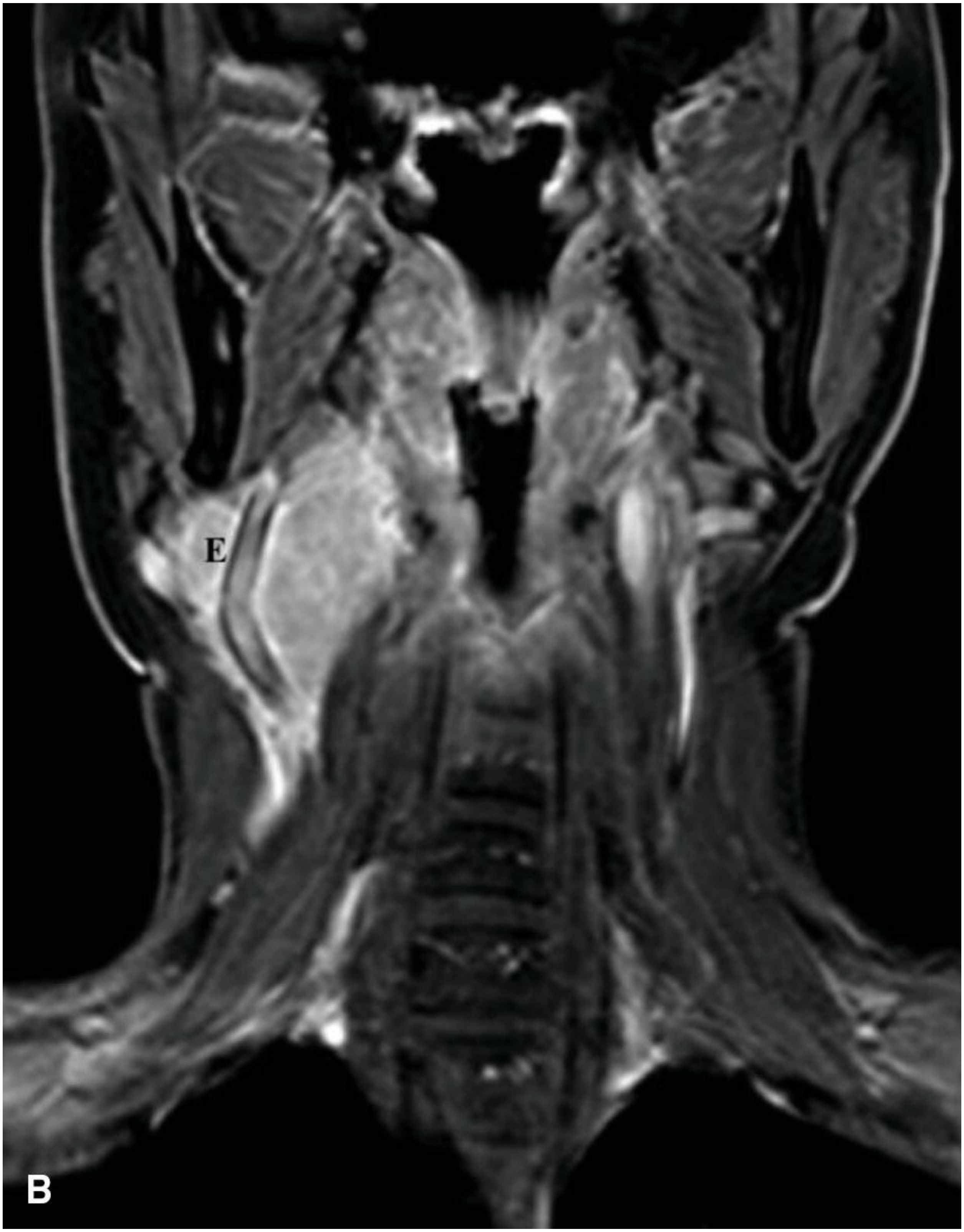
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Figure 22.10. Large carotid body tumor (Shamblin type III). T1-weighted postcontrast MRI axial images demonstrate large avidly enhancing mass in

the right carotid space, splaying the external carotid artery (*E*) anteriorly and the internal carotid artery (*I*) posteriorly **(A, B)**. Angiography image **(C)** in right lateral view shows widening of the carotid bifurcation by vascular tumor (i.e., Lyre sign) supplied by multiple hypertrophied vessels, predominantly arising from the external carotid artery (*E*).

Treatment decisions for paragangliomas are challenging and require the input from a multidisciplinary team of specialists familiar with these tumors. Treatment may include observation, surgery, or radiation therapy. Although traditionally these tumors have been treated with surgery, both conventional radiation therapy and stereotactic radiation therapy have been shown to be effective in either stabilization or decreasing tumor volume.[28,29] Long-term local control rates in excess of 94% have been reported, and overall survival is comparable to that of surgical excision.[28] Reported complications following radiation therapy have included headaches, xerostomia, mucositis, transient cranial nerve palsies, hearing loss, and dysequilibirum.[28] The distinction between malignant and benign paragangliomas can only be made on the basis of nodal or distant metastasis, as there are no distinguishing histopathologic features at the primary site. On this basis, about 7% of paragangliomas meet the criteria for malignancy.[30,31] On sequential radiologic imaging, between 25% and 40% of paragangliomas in the head and neck have been shown to remain stable in size, whereas those that enlarged grew at a median rate of ~1 to 2 mm/year, which makes observation a reasonable option for select patients.[32,33]

In those patients undergoing surgery with tumors generally larger than 3 cm, arteriography with preoperative embolization of carotid body tumors has been used as a treatment strategy to minimize intraoperative blood loss (Fig. 22.11). In one study, 131 patients with Shamblin class II and III tumors were divided into a presurgery embolization group and nonembolization group. Presurgery embolization was shown to reduce intraoperative blood loss and the need for intraoperative ICA clamping but did not reduce the rates of cranial nerve injury, stroke, or death.[34] No significant differences in the distribution of tumor size were found to exist between groups. The optimal timing for surgical resection following embolization has not been determined, but surgical resection following embolization should generally occur within 24 hours.[35] The preoperative management of catecholamine-secreting carotid

body tumor (CBT) should also include endocrinologists and anesthesiologists for a comprehensive cardiac workup and titration of alpha-adrenergic blockade. Surgical principles for excision of carotid body tumors include proximal and distal control of the carotid artery and identification and preservation of the spinal accessory and hypoglossal and vagus nerves prior to dissection of the tumor in a subadventitial plane (Fig. 22.12).


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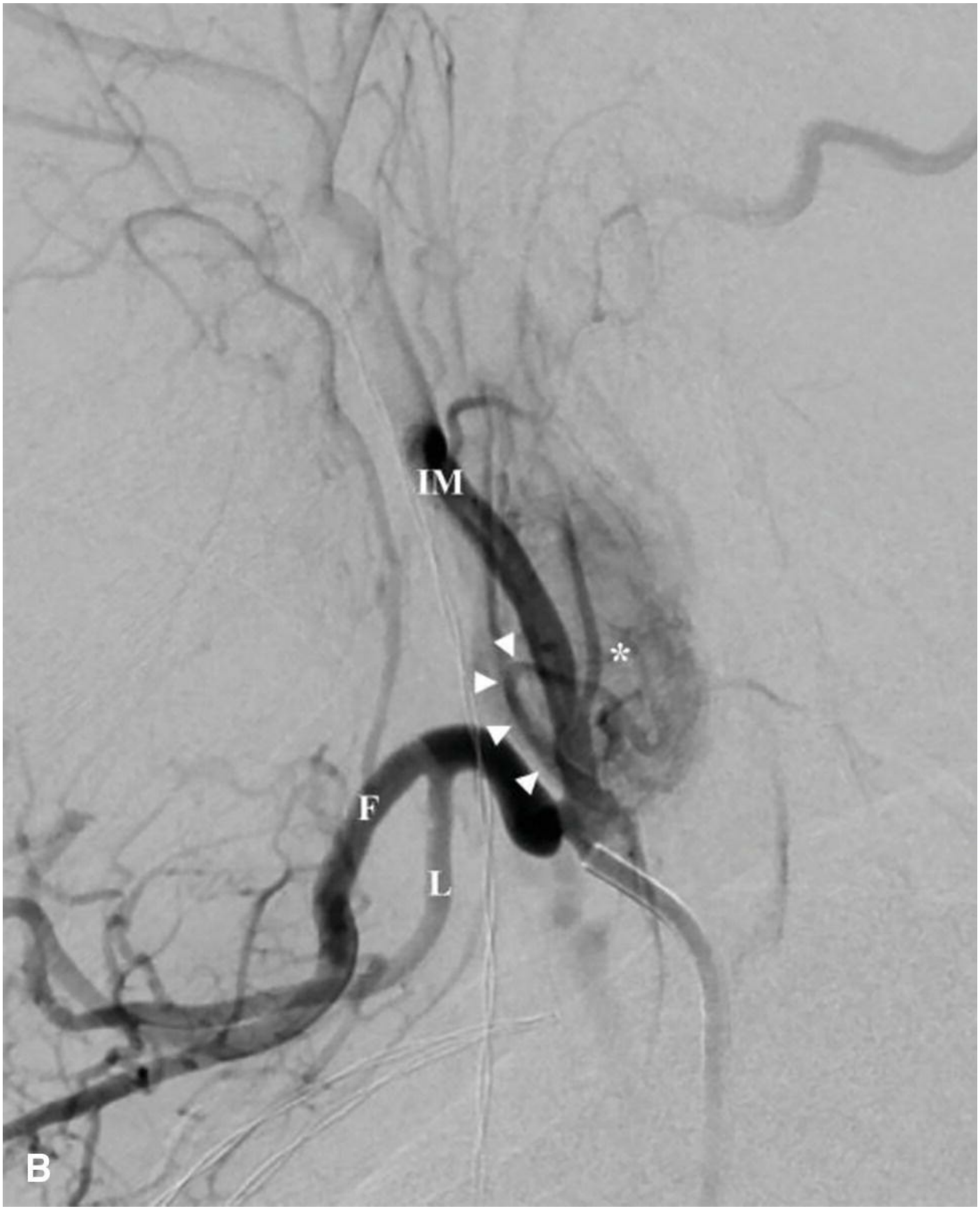
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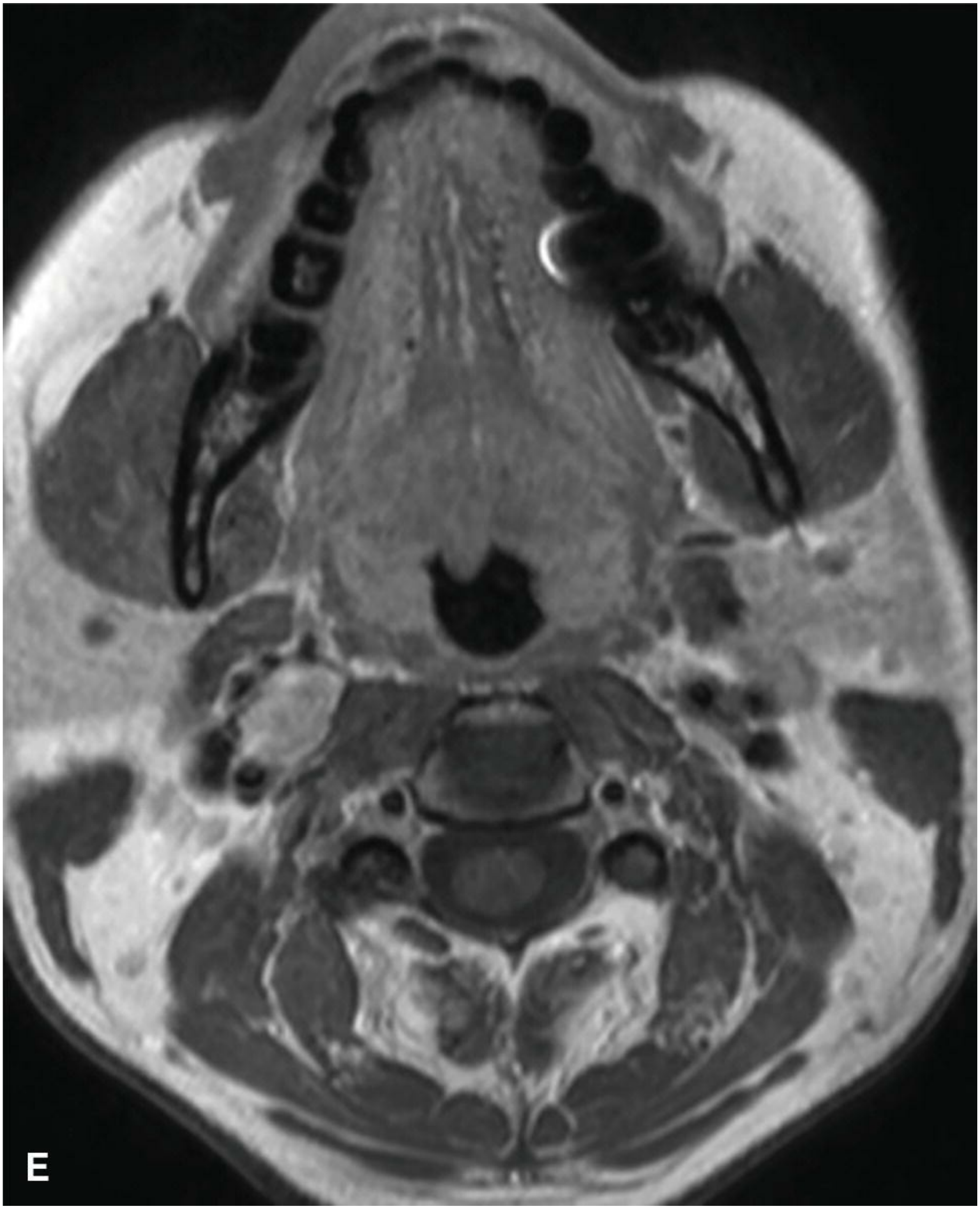
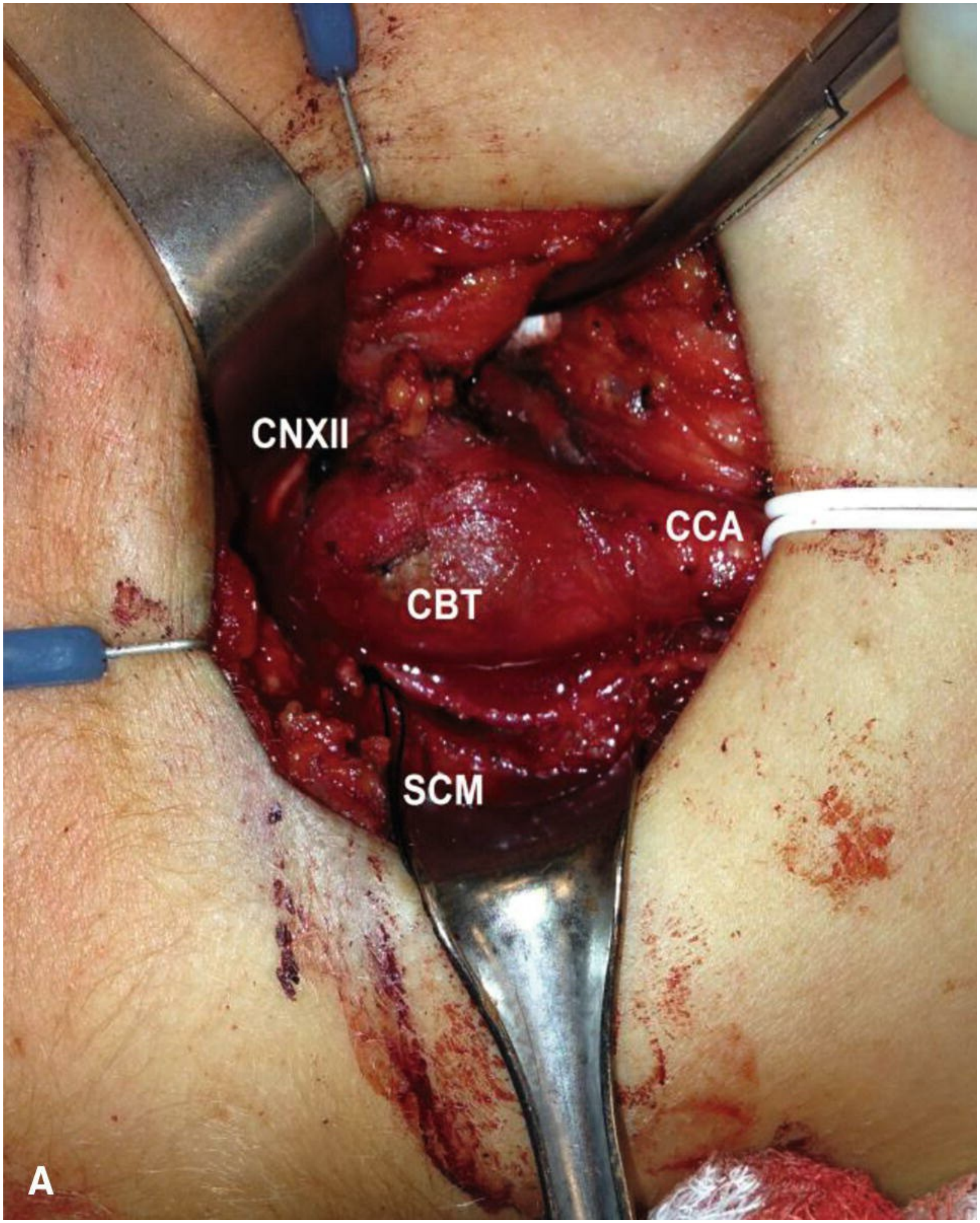


Figure 22.11. Embolization of paraganglioma (*asterisk*). **A:** Common carotid angiogram (*I*, internal carotid artery; *E*, external carotid artery) with vascular tumor (*asterisk*) just above the carotid bifurcation. **B:** External carotid

angiogram demonstrates supply of the tumor by ascending pharyngeal branch (*arrowheads*) (*IM*, internal maxillary artery; *F*, facial artery; *L*, lingual artery). **C:** Microcatheterization of the ascending pharyngeal branch (*arrowheads*) for infusion of embolizing microspheres. **D:** Postembolization external carotid angiogram demonstrates markedly reduced perfusion to the tumor (*asterisk*).
Figure 22.11.(Continued)

E:T1-weighted postcontrast image of the enhancing tumor in right poststyloid PPS.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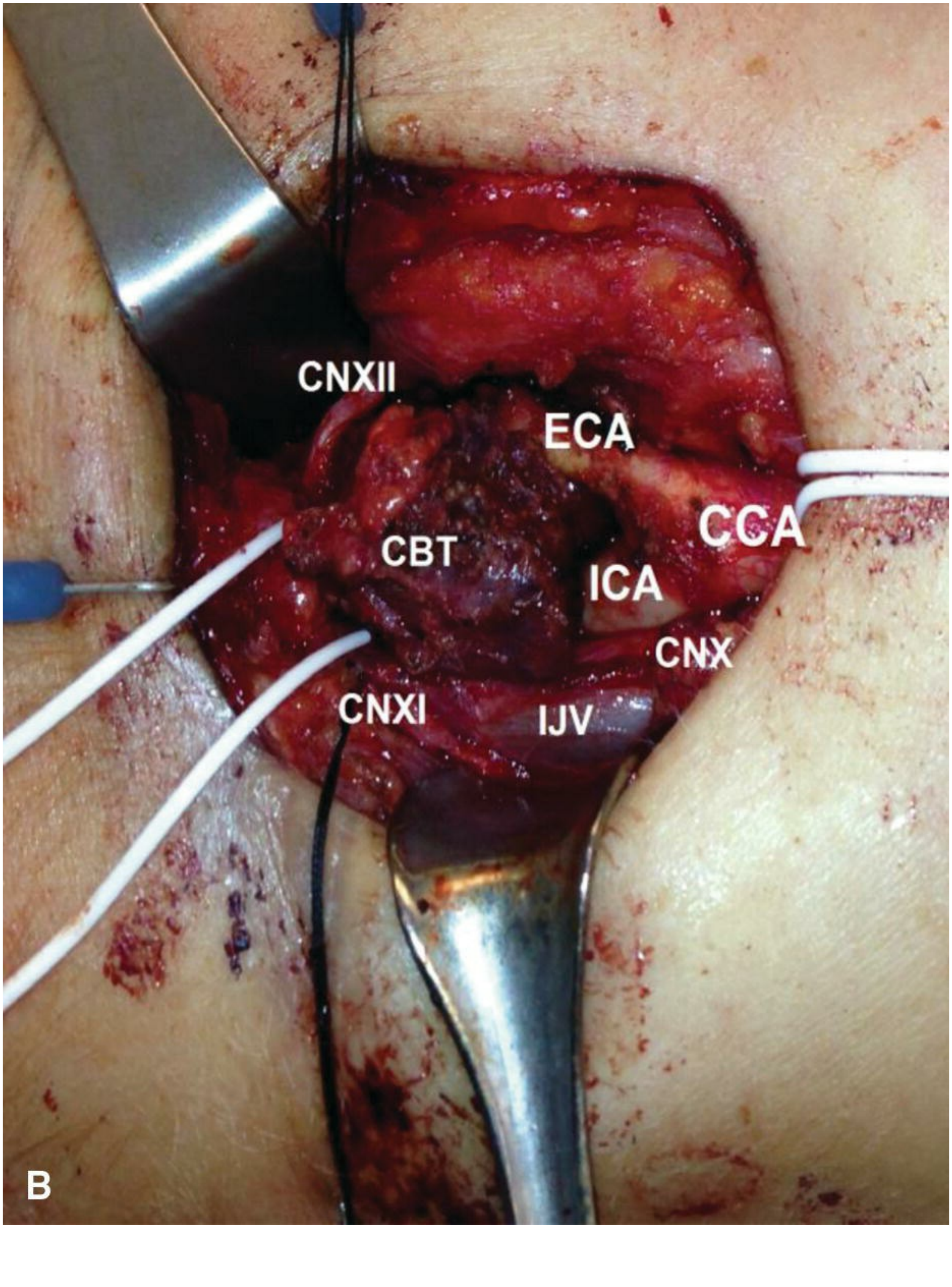
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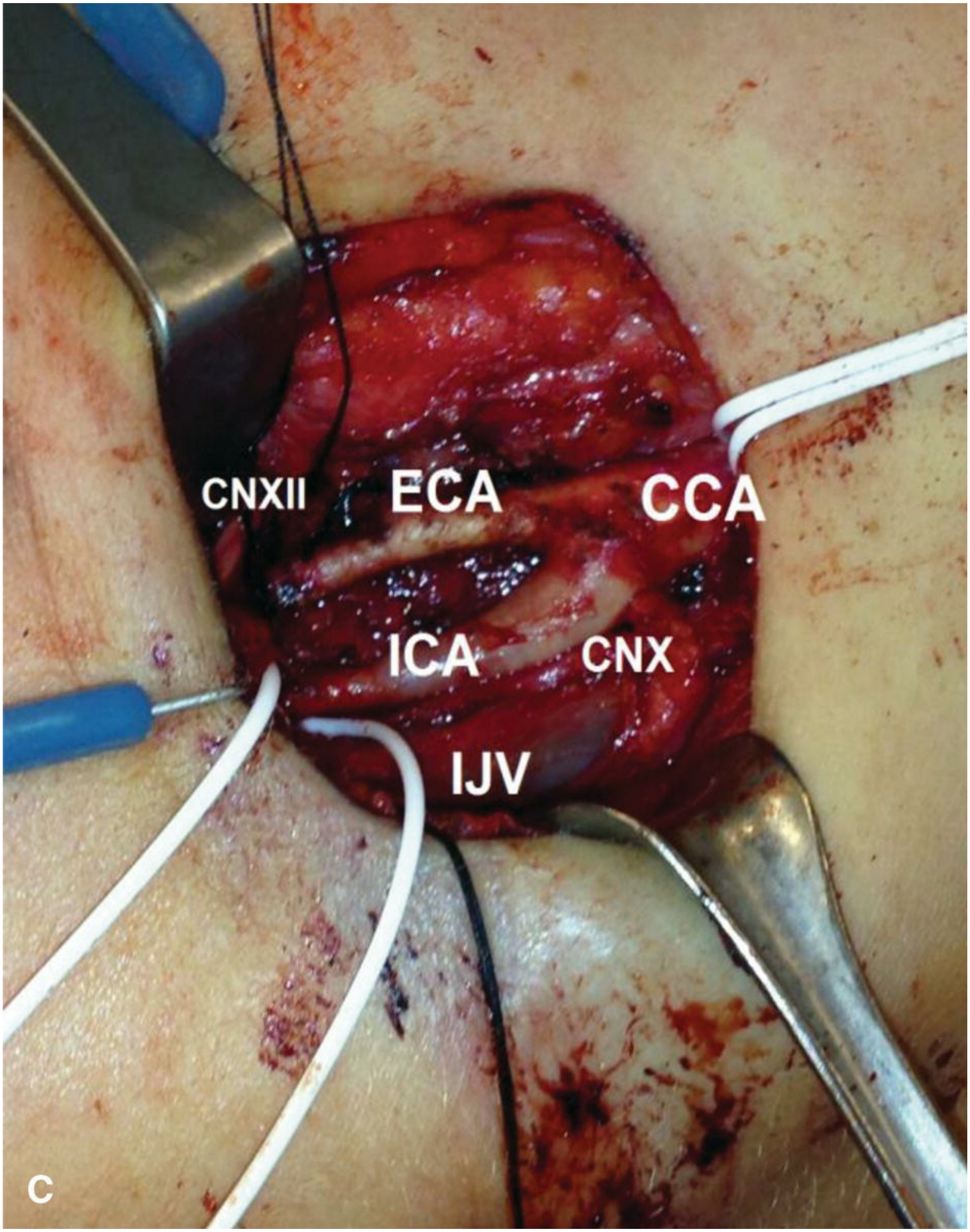


Figure 22.12. Excision of a carotid body tumor. **A:** Initial exposure of carotid body tumor. **B:** Subadventitial dissection of carotid body tumor following

proximal and distal control of internal carotid artery. **C:** Preservation of neurovascular structures following excision of carotid body tumor. *CCA*, common carotid artery; *ICA*, internal carotid artery; *ECA*, external carotid artery; *CBT*, carotid body tumor; *CNX*, vagus nerve; *CNXI*, spinal accessory nerve; *CNXII*, hypoglossal nerve; *SCM*, sternocleidomastoid muscle.

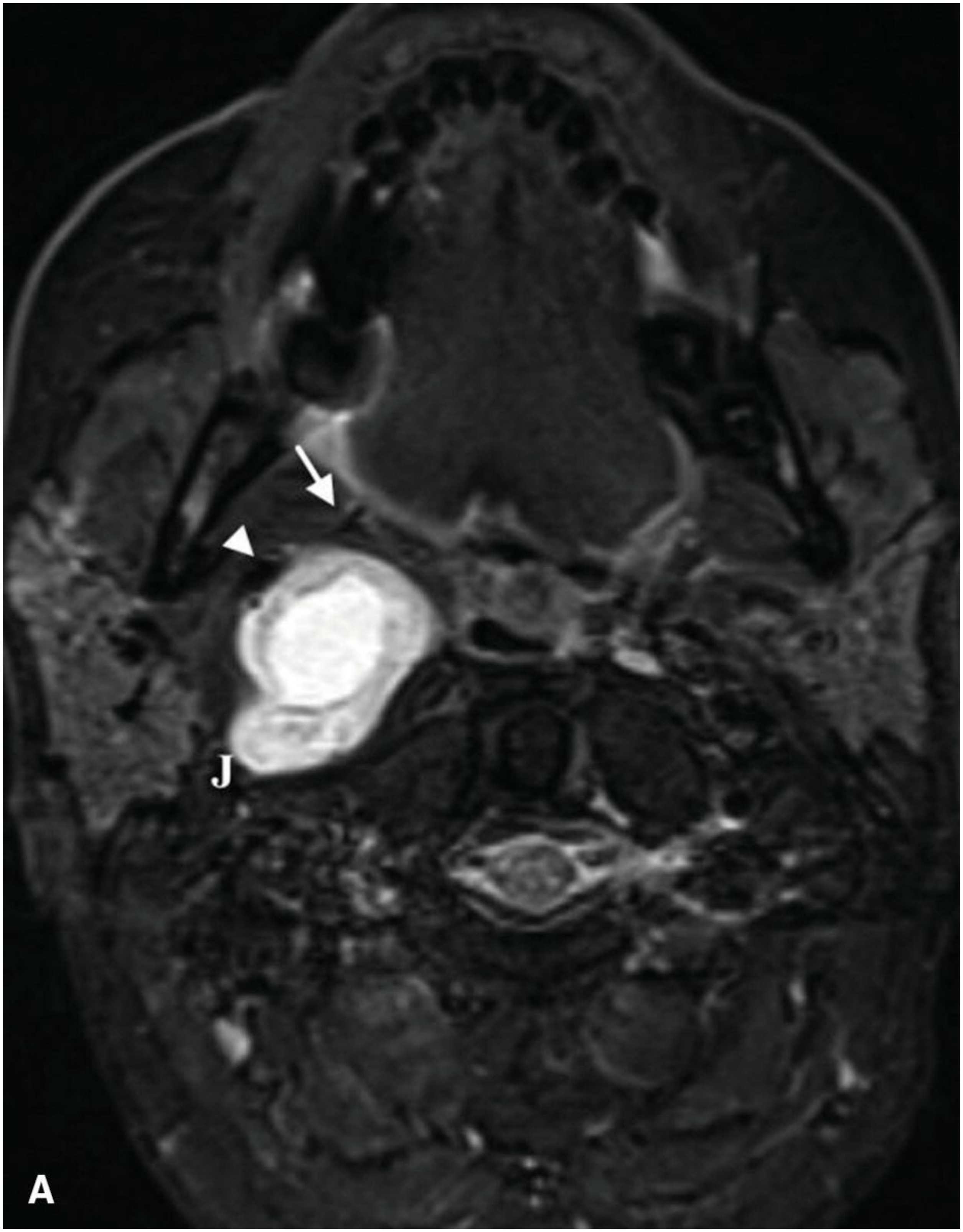
Nonsurgical options for management of metastatic paraganglioma that have been used include ^{131}I-MIBG therapy, combination chemotherapy with cyclophosphamide, vincristine and dacarbazine, and sunitinib, a tyrosine kinase inhibitor.[36,37] A recent meta-analysis of studies using ^{131}I-MIBG therapy for treatment of metastatic paraganglioma and pheochromocytoma in 243 patients demonstrated stable disease in 50% of patients over a mean duration follow-up period of between 24 and 62 months.[38] Eligibility for ^{131}I-MIBG therapy is dependent on demonstration of adequate radiotracer uptake on pretreatment scintigraphy.

Neurilemmoma

Nonvestibular neurilemmomas, also known as schwannomas of the head and neck, most frequently occur in the PPS. These benign tumors arise from the neuroectodermal nerve sheath of a peripheral nerve. Histologically, they exhibit two different patterns as described by Antoni in 1920. In the “Antoni A” pattern, a distinctive pattern of spindle-shaped cells known as Verocay bodies is arranged in a stacked palisading pattern alternating with anuclear zones containing cellular cytoplasm. In the Antoni B pattern, cells are arranged in a random pattern within a loose myxoid stroma. On immunohistochemistry, these tumors stain intensely for the S100 protein. Within the PPS, most schwannomas are of either vagal or cervical sympathetic chain origin, and although the vast majority of these tumors are benign, malignant degeneration has been described. It is difficult to determine the nerve of origin based solely on the patient’s history and clinical examination alone due to the nonspecificity of the presenting symptoms.

With regard to their radiologic appearance, they are ovoid to fusiform in shape with smooth, well-defined margins. On MRI T1 sequences, neurilemmomas most commonly have low signal intensities, whereas on T2 sequences, these tumors have a higher intensity compared to surrounding muscle. With administration of contrast, they show uniform enhancement but

do not demonstrate flow voids and are less vascular compared to paragangliomas. Determining the nerve of origin is possible by identifying the relationship of the tumor to the ICA and the IJV. In vagus nerve schwannomas, the tumor usually causes separation of the ICA and IJV (Figs. 22.13 and 22.14), whereas in a cervical sympathetic schwannoma, both ICA and IJV are typically displaced together without separation.[39,40] Splaying of the ICA and external carotid artery by a cervical chain sympathetic schwannoma has also been described.[41] This can be explained by the posteromedial relation of the cervical sympathetic trunk to the ICA at the level of the carotid bifurcation, with nondistensible boundaries of the cervical vertebra column medially and the longus capitis muscle posteriorly, whereas vagal nerve fibers course lateral to the ICA.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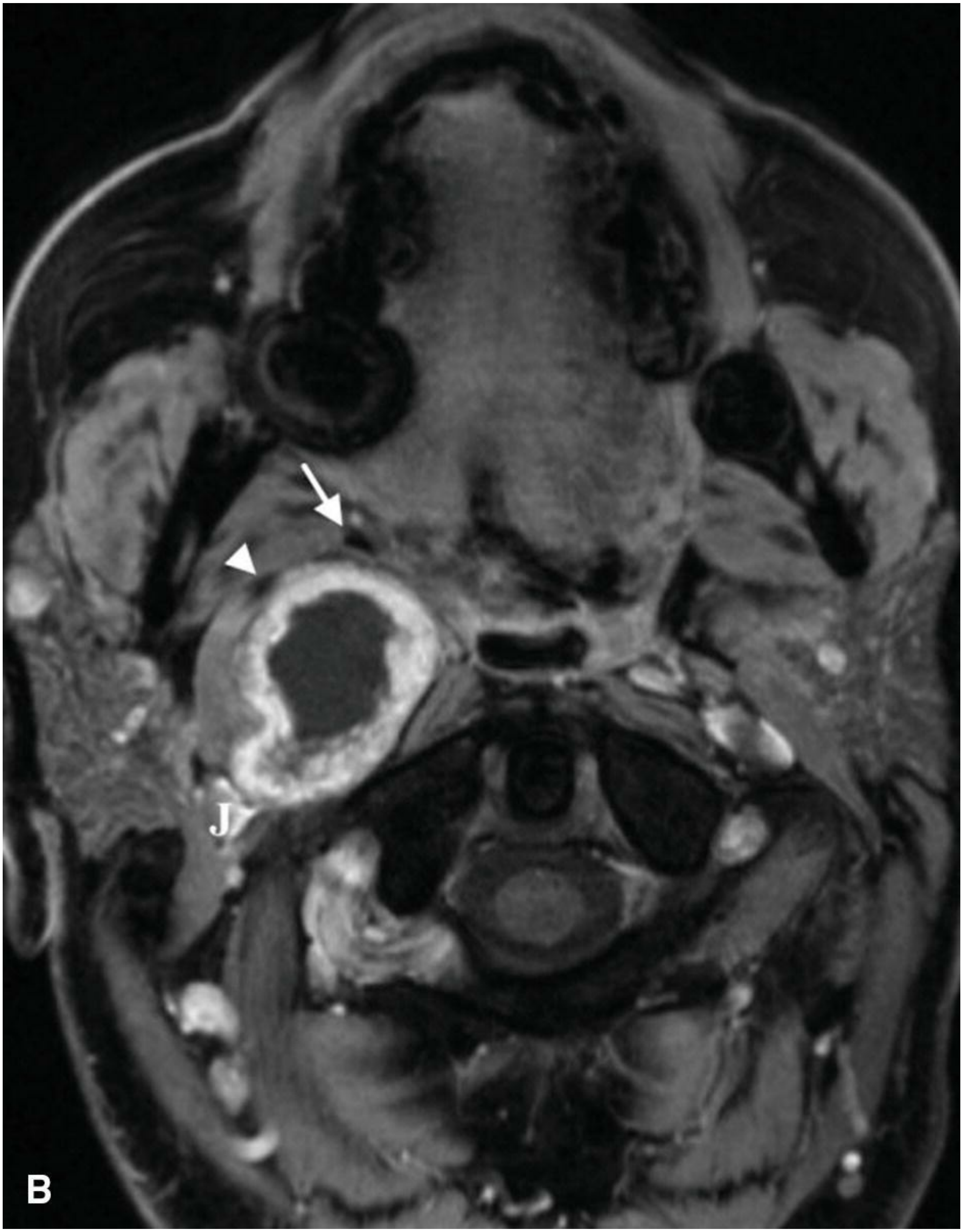
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Figure 22.13. Schwannoma (cystic). A 57-year-old woman a with PPS mass incidentally noted on spinal MRI. Ring enhancing, a primarily cystic mass

lesion arising within the right poststyloid PPS with its superior margin at the inferior jugular foramen. The mass displaces the internal (*arrow*) and external carotid (*arrowhead*) arteries anteriorly away from the internal jugular vein (*J*). Imaging characteristics are most suggestive of a suprahyoid vagus nerve schwannoma. When noncystic, schwannoma may be differentiated from vagal paraganglioma by lack of flow voids and less rapid enhancement on dynamic imaging. **A:** T2-weighted image. **B:** T1-weighted axial postcontrast image. **C:** T1-weighted coronal postcontrast image.

A

Figure 22.14. Schwannoma (noncystic). Circumscribed T2 hyperintense enhancing mass in the right poststyloid PPS. This tumor displaces the internal carotid artery (*I*) laterally, a pattern atypical for schwannoma. **A:** T1-

weighted postcontrast image without adipose tissue suppression demonstrates displacement of the prestyloid parapharyngeal adipose anteriorly (*arrowheads*). **B:** Coronal T1-weighted postcontrast image.

These tumors are relatively radioresistant, so that complete surgical resection is the definitive treatment, although given the slow rate of growth and noninvasive nature of these tumors; observation with serial imaging is another management option. Intracapsular tumor excision is a surgical technique that allows for preservation of nerve continuity, although structural nerve continuity following complete tumor excision does not always equate to normal functioning. The epineurium of the nerve is incised longitudinally, and blunt dissection is carried out parallel to nerve fibers teasing the tumor from within the nerve. Alternatively, microdebrider or coblation may be employed to decompress the tumor and facilitate excision. Preservation of nerve function following this technique has been reported to range from 78% to 85% in two recent case series.[42,43]

Neurofibroma

Neurofibromas are benign peripheral nerve tumors arising from nonmyelinating Schwann cells. Histologically, the neoplastic cells, which have elongated wavy, twisted nuclei, are intimately involved with axons in a myxoid matrix containing thin walled vessels, mast cells, and fibroblasts. Neurofibromas stain for S100 protein, neurofilament protein, and myelin basic protein. A clear histologic distinction between neurofibromas and schwannomas is sometimes difficult, although schwannomas exhibit an Antoni A or Antoni B pattern, have a more diffuse staining pattern for the S100 protein, and do not usually stain for neurofilament protein.

Radiologically, neurofibromas have similar imaging characteristics as other neural crest-derived tumors including schwannomas and ganglioneuromas, appearing hypo- to isointense on T1-weighted images and hyperintense on T2-weighted images. Distinguishing between these tumors is often difficult on radiologic interpretation alone, as demonstrated on Figure 22.15. Features that have been proposed to distinguish neurofibromas from schwannomas include a “target sign” on T2-weighted imaging, manifesting as a hypointense central area in an otherwise hyperintense periphery and tumor bulk occupying a central position within the nerve of origin, in contrast

to schwannomas, which more frequently have an eccentric relation to the nerve of origin.[44]


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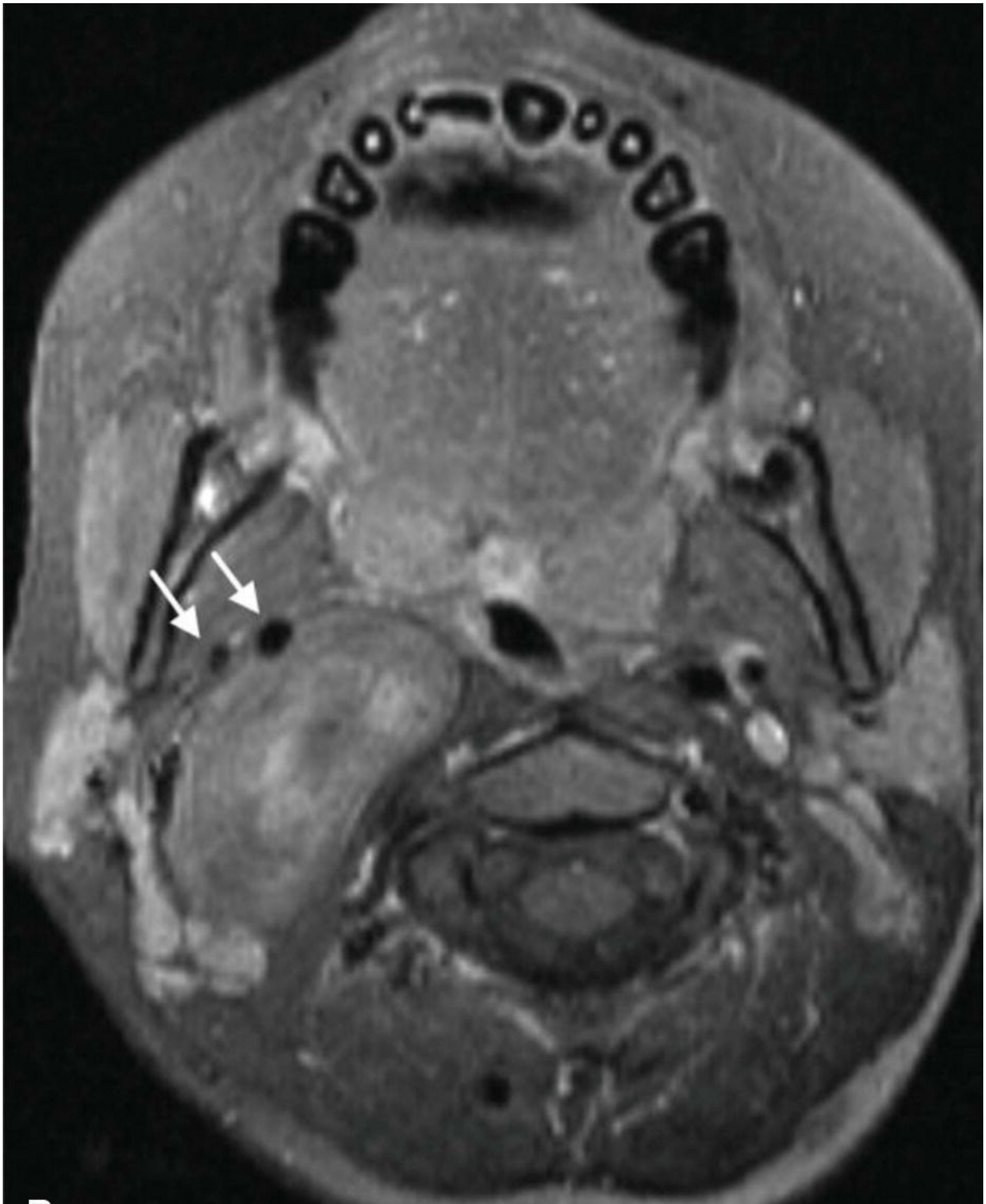
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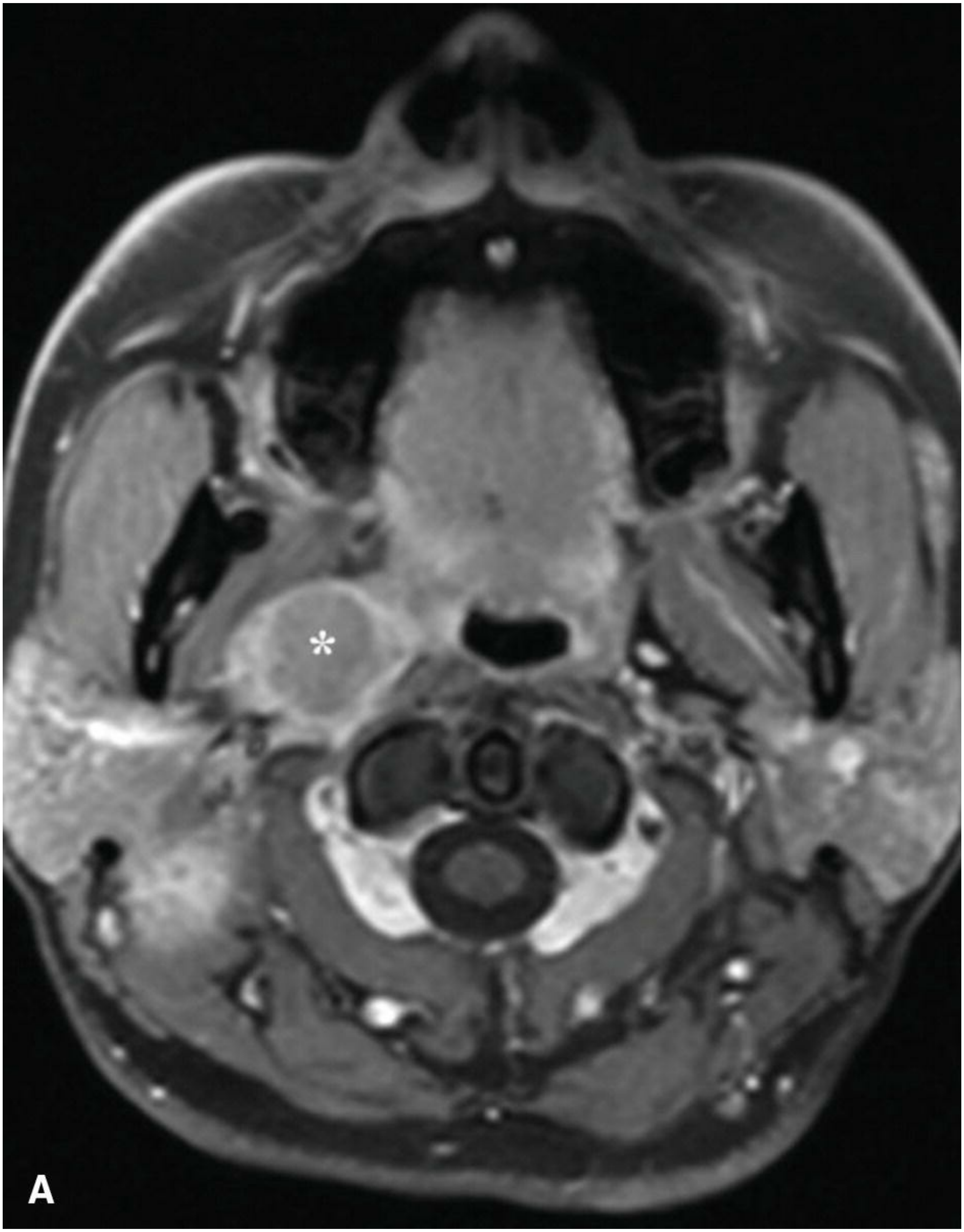
Figure 22.15. Ganglioneuroma. A heterogeneous T2 hyperintense mass with heterogeneous enhancement arising from the poststyloid PPS, displacing both

carotid vessels anteriorly (*arrows*) just above the bifurcation. Imaging characteristics are similar to neurofibroma, but pathology on excision demonstrated ganglioneuroma. **A:** T2-weighted MRI. **B:** axial T1-weighted postcontrast image. **C:** Coronal T1-weighted postcontrast image.

Multiple neurofibromas occur in association with von Recklinghausen disease (neurofibromatosis type I), an autosomal dominant inherited disorder with low penetrance occurring in 1 per 3,000 births. Mutations in the NF1 gene, which is a tumor suppressor gene involved in the production of neurofibromin, have been attributed to this disease. Clinical characteristics of neurofibromatosis Type I include multiple café au lait spots, Lisch nodules, and optic gliomas. Malignant degeneration occurs more commonly in neurofibromatosis type I and is rare in patients with solitary neurofibromas. Histologic features of malignancy include pleomorphic nuclei, increased mitotic activity, and hypercellularity, whereas clinical features include rapid increase in size, cranial nerve deficits, and metastasis. Similar to schwannomas, neurofibromas are relatively radioresistant, and surgical excision versus observation are the major management options.

OTHER TUMORS OF THE PARAPHARYNGEAL SPACE

The lymphatics within the PPS receive drainage from the oral cavity, oropharynx, nasopharynx, and thyroid gland. As such, metastasis from these regions has been described including papillary thyroid cancer, medullary thyroid cancer, squamous cell carcinoma, and nasopharyngeal carcinoma (Fig. 22.16). Non-Hodgkin lymphoma occurs very rarely in the PPS and is treated primarily with radiotherapy or concurrent chemoradiation, depending on the stage of the tumor.[45] Lipomas are also rare benign tumors of mesenchymal origin that show a characteristic well-defined, lobulated, nonenhancing hyperintense signal on T1-weighted imaging.[46] Management options for these tumors are surgical excision versus observation. Congenital lesions such as 2nd branchial cleft cysts can manifest in the PPS (Fig. 22.17), with MRI findings showing well-marginated, cystic masses showing mild hyperintensity on T1-weighted imaging and mild hypointensity on T2-weighted imaging compared to cerebrospinal fluid.[47]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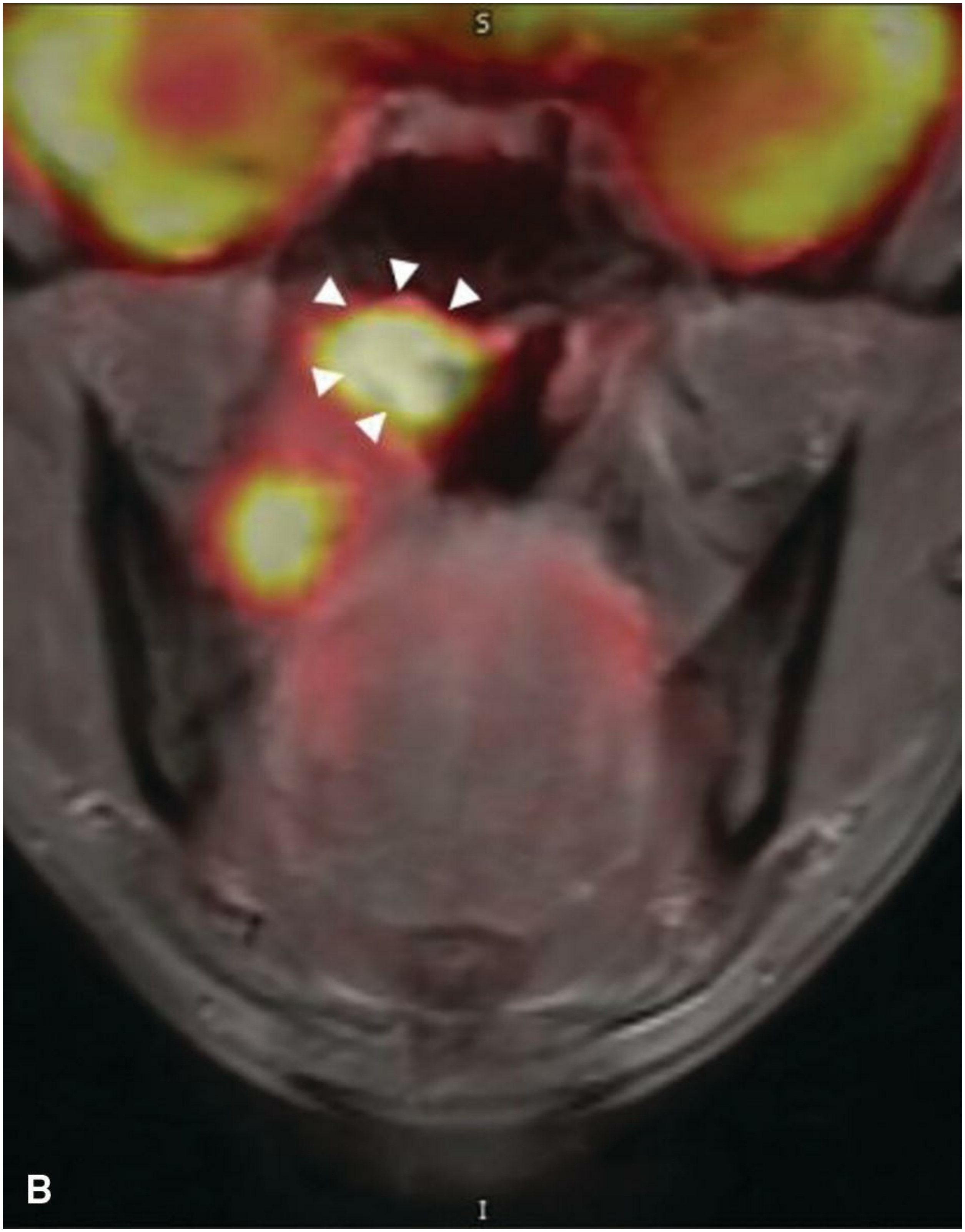
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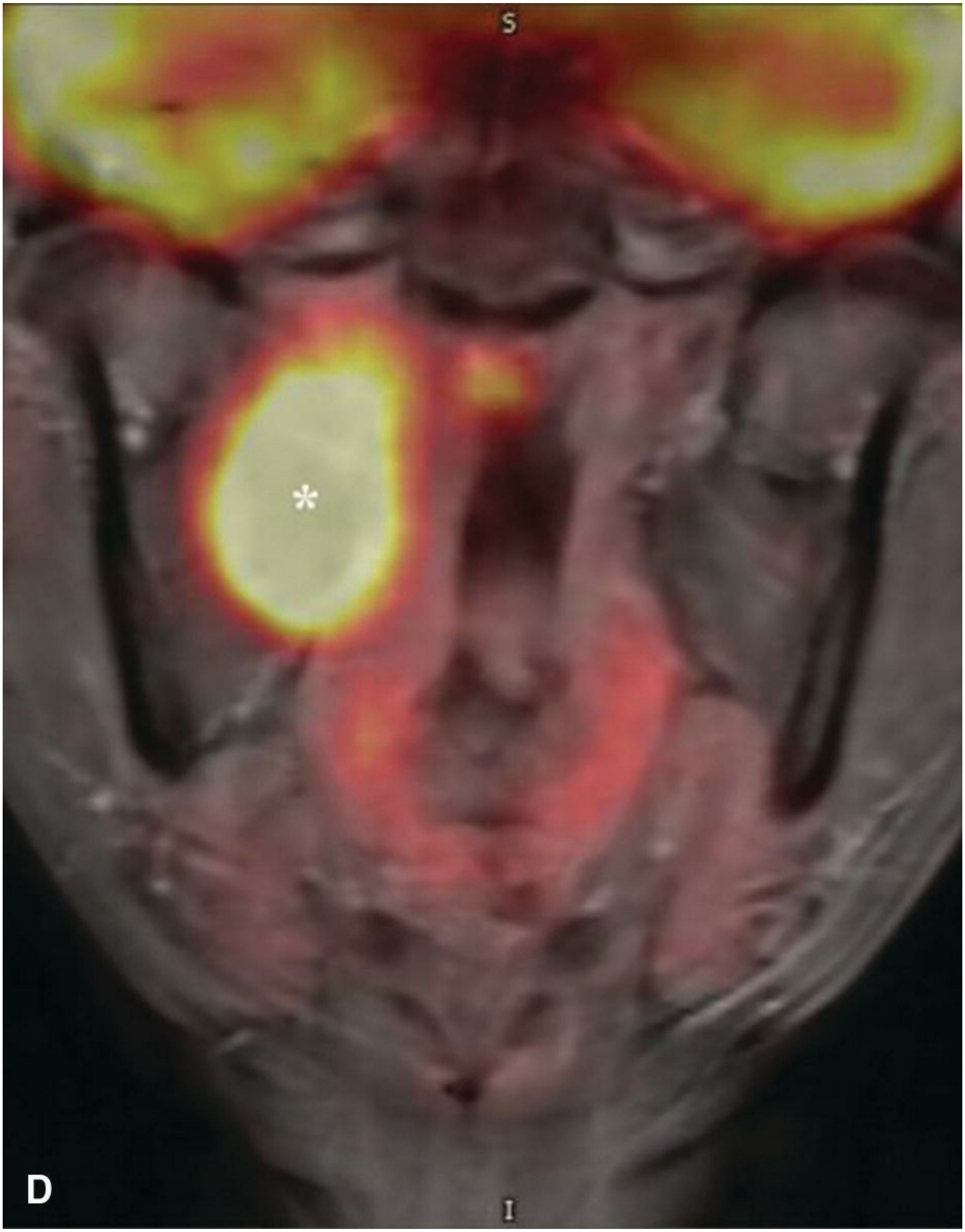
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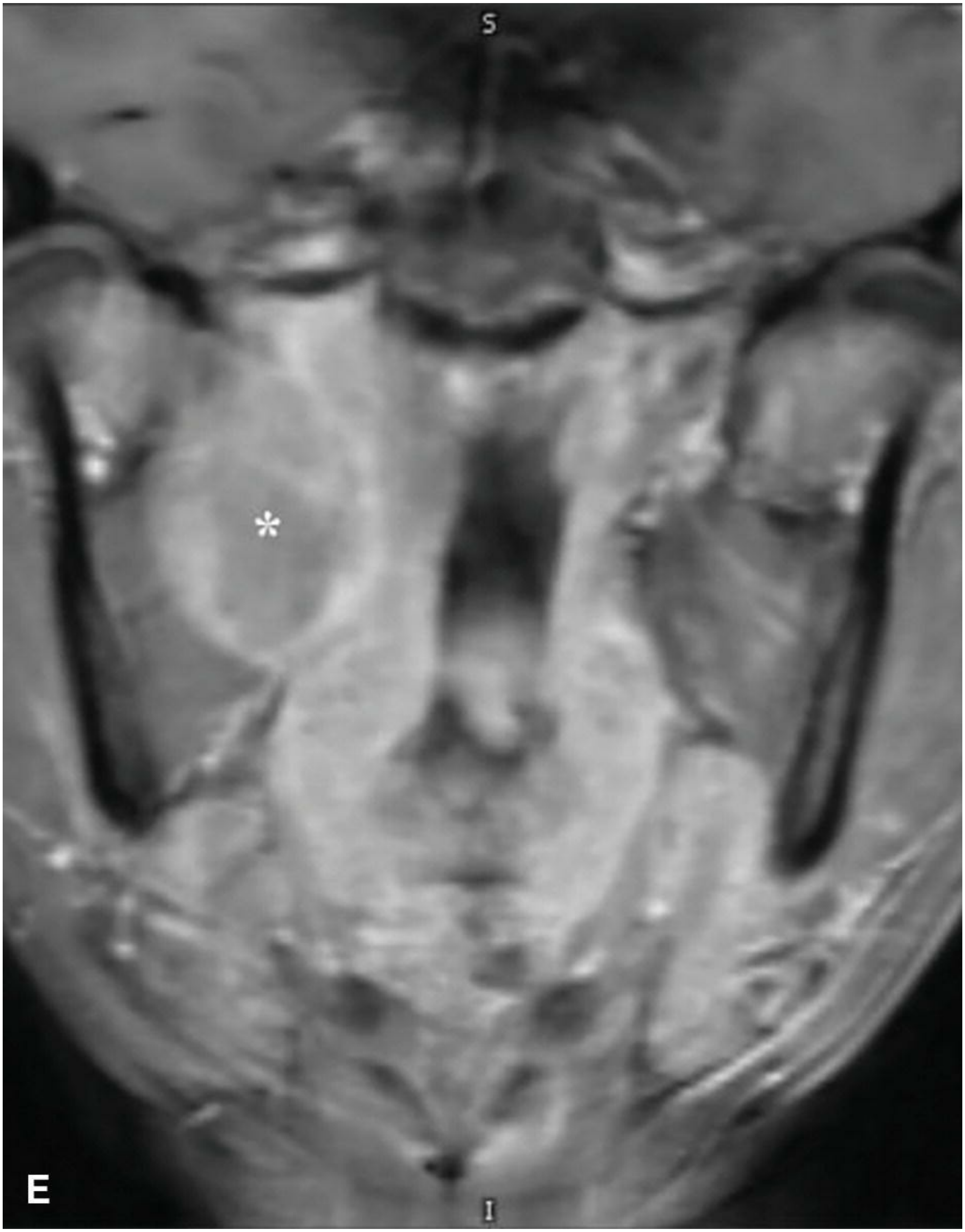

Figure 22.16. Malignant adenopathy. A 41-year-old woman who presented with a mass in the left neck and was found to have nasopharyngeal carcinoma

with malignant lymphadenopathy extending to the PPS. **A:** Postcontrast T1-weighted MR image showing peripherally enhancing malignant adenopathy (*asterisk*) obliterating the space normally occupied by parapharyngeal fat. **B–E:** Coronal images from software fusion of PET and postcontrast MRI demonstrating intensely FDG-avid primary tumor in the nasopharynx (*arrowheads*) and parapharyngeal adenopathy (*asterisk*).

Figure 22.17. Branchial cleft cyst. Neonate with left neck mass. Contrast-enhanced CT demonstrates large hypodense cystic lesion in the left PPS. The walls of the cyst are nonenhancing, and the carotid sheath contents are

displaced laterally. This is most likely a branchial cleft cyst, with differential also including laryngocele and rare pharyngeal/esophageal duplication cyst.

SURGICAL APPROACHES

The general principles that should be adhered to in the resection of PPS tumors are maximization of intraoperative exposure to allow for safe dissection of the tumor with adequate margins, visualization of critical neurovascular structures, and minimization of functional and cosmetic morbidity.

Transcervical Approach

This is the most commonly used surgical approach to the PPS (Fig. 22.18).[9,48,49] The advantages to this approach include clear visualization of major blood vessels and nerves, no oral flora contamination, maintenance of sterility, and cosmesis with the incision placed in a natural skin crease. The limitations to this approach include poor visualization of the superior and medial aspect of tumors in close proximity to the skull base and inability to identify and protect proximal facial nerve branches in tumors involving the deep lobe of the parotid gland. The skin incision is most commonly placed in a natural skin crease several fingerbreadths below the mandible. Subplatysmal flaps are raised, followed by identification and preservation of the marginal mandibular branch of the facial nerve. The anterior border of the sternocleidomastoid muscle and digastric and stylohyoid muscles is then identified. Access to the PPS is obtained through superior retraction of the mandibular body and inferior retraction of cervical tissue. Exposure to the PPS through this route can be improved through division of the stylomandibular ligament and digastric and stylohyoid muscles. Removal of the submandibular gland is not usually necessary.


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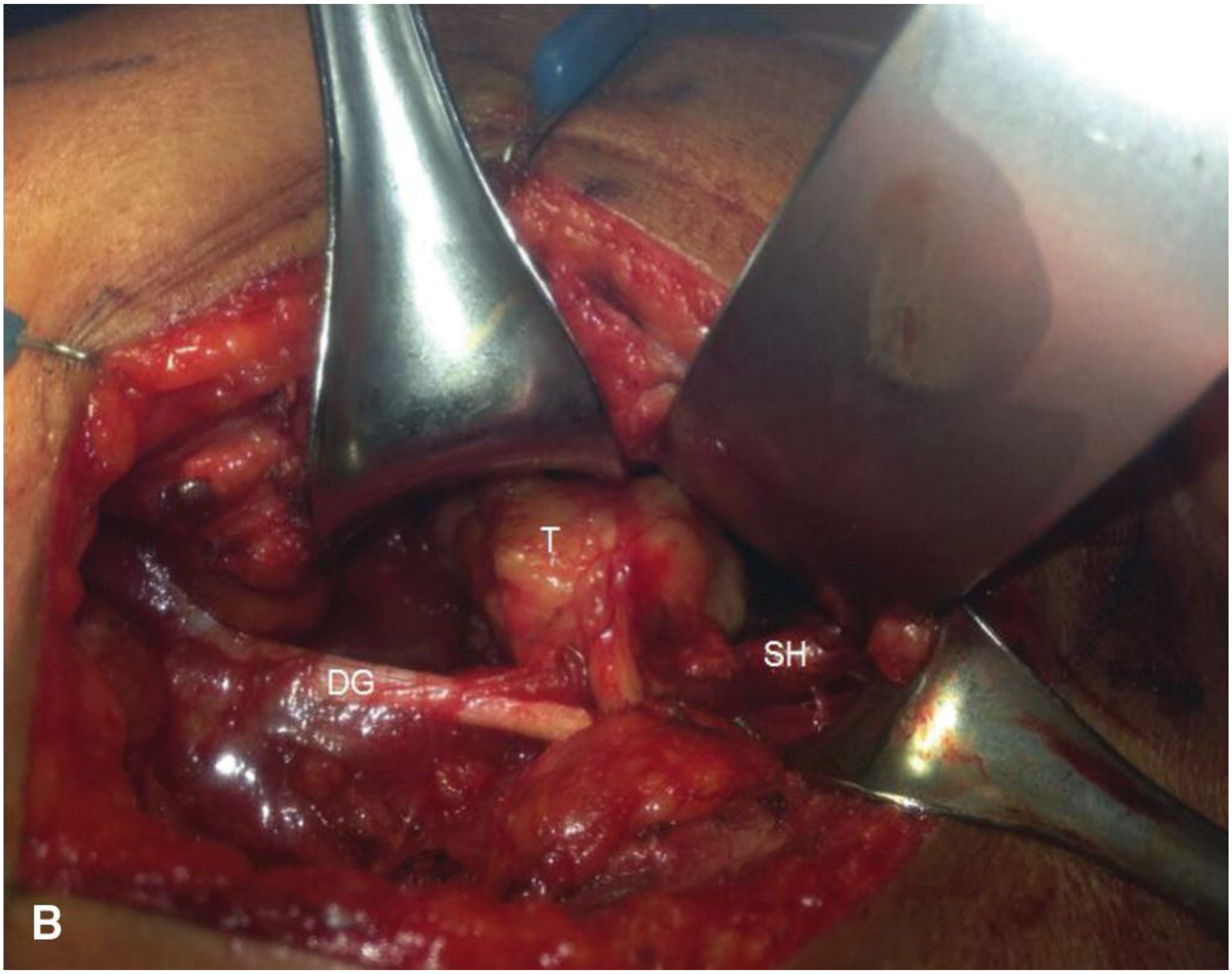
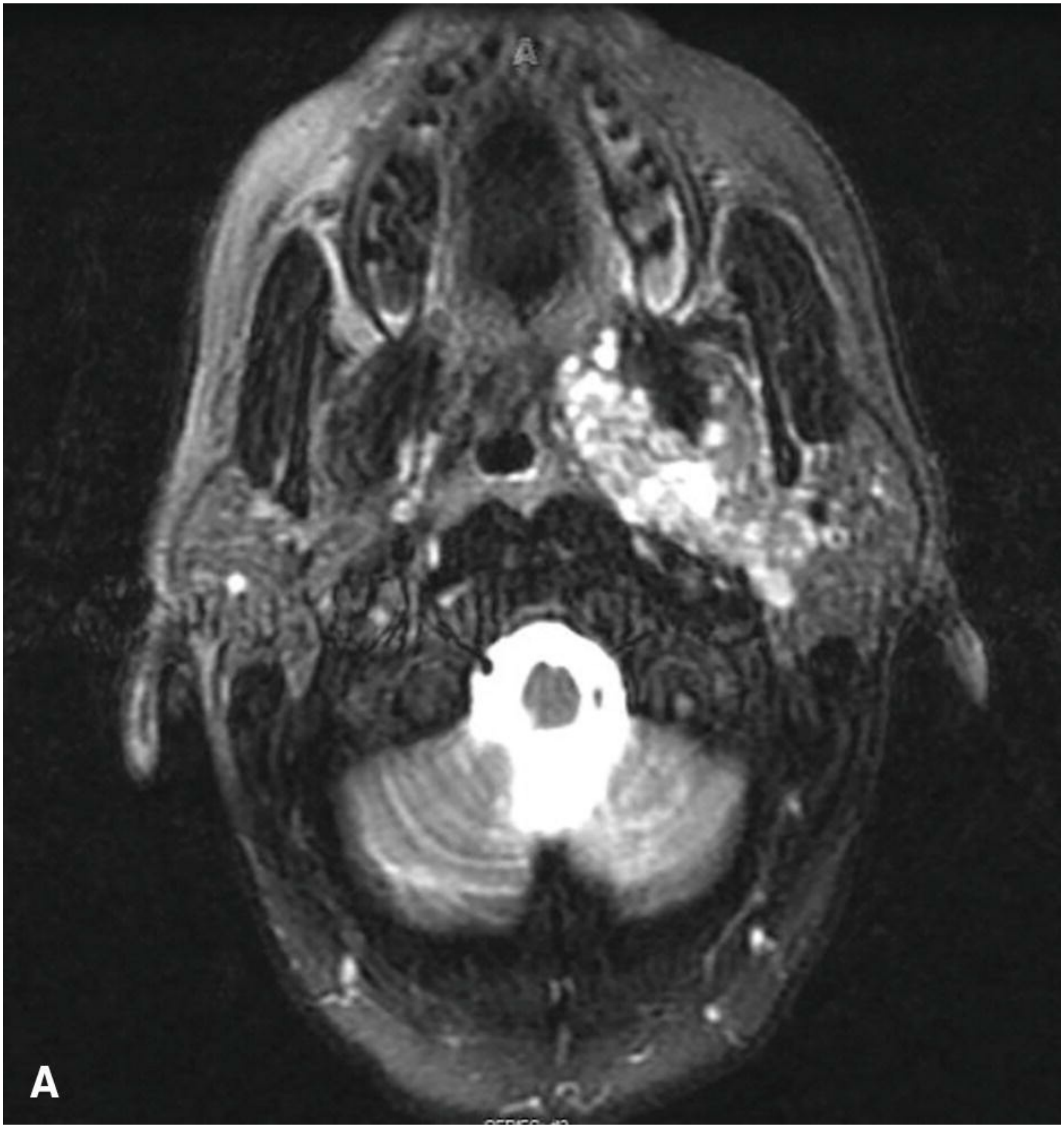


Figure 22.18. Transcervical approach for resection of a deep lobe pleomorphic adenoma. **A:** Planned cervical incision in a natural skin crease below the inferior edge of the mandible. **B:** Subplatysmal flaps have been elevated, the submandibular gland is retracted anteriorly, the posterior belly of the digastric (*DG*) and stylohyoid (*SH*) muscle has been identified, and superior retraction of the mandibular body after sectioning the stylomandibular ligament reveals the pleomorphic adenoma (*T*).

Postoperative complications with this approach include temporary pain in the jaw and transient marginal mandibular nerve weakness.[48] Visualization within the PPS from a transcervical approach can be facilitated using endoscopes, especially along the superomedial dissection. A visible cervical scar can also be avoided by using a hairline incision or facelift approach.

Transcervical–Transparotid Approach

The transcervical–transparotid approach is used for deep lobe parotid neoplasms extending into the prestyloid PPS (Fig. 22.19). A key feature of this approach is formal identification and preservation of the main trunk of the facial nerve to enable safe dissection of the tumor medial to the nerve. A modified Blair incision is carried out in a preauricular skin crease and extended inferiorly to incorporate a natural cervical skin crease. Anterior and posterior flaps are raised in a fashion similar to a parotidectomy. The anterior border of the sternocleidomastoid muscle in level II is skeletonized, allowing for identification of the posterior belly of the digastric muscle, which establishes the approximate depth of the facial nerve. Dissection in a broad plane separating parotid tissue from the tragal cartilage enables identification of the tragal pointer and tympanomastoid suture line that are useful landmarks to find the facial nerve. Once the facial nerve is identified, branches of the facial nerve are traced distally and dissected away from the underlying tumor capsule. Anterior retraction of the submandibular gland allows mobilization of the inferior aspect of the tumor. Division of the stylomandibular ligament and mandibulotomy are additional steps to improve tumor access.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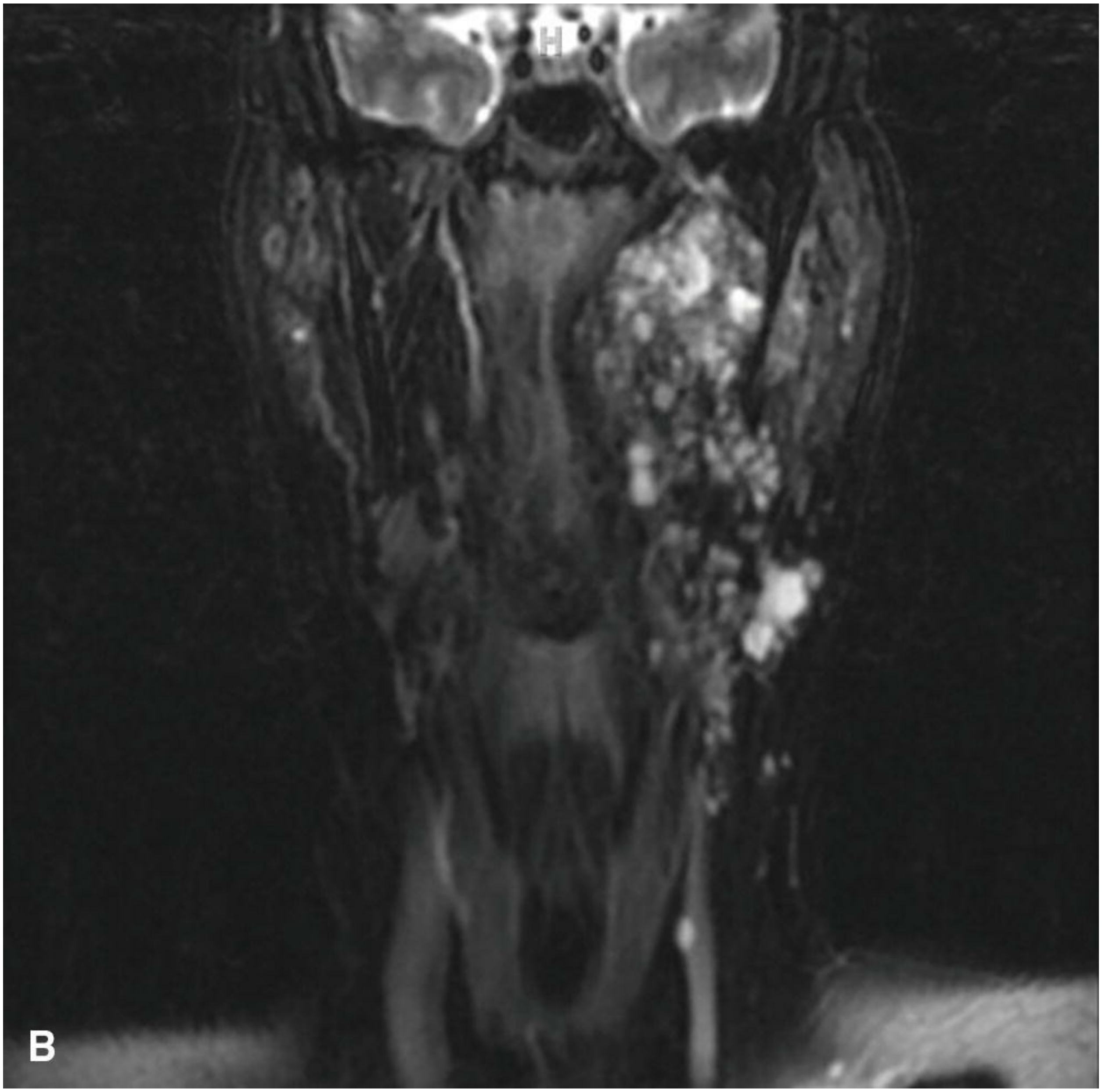
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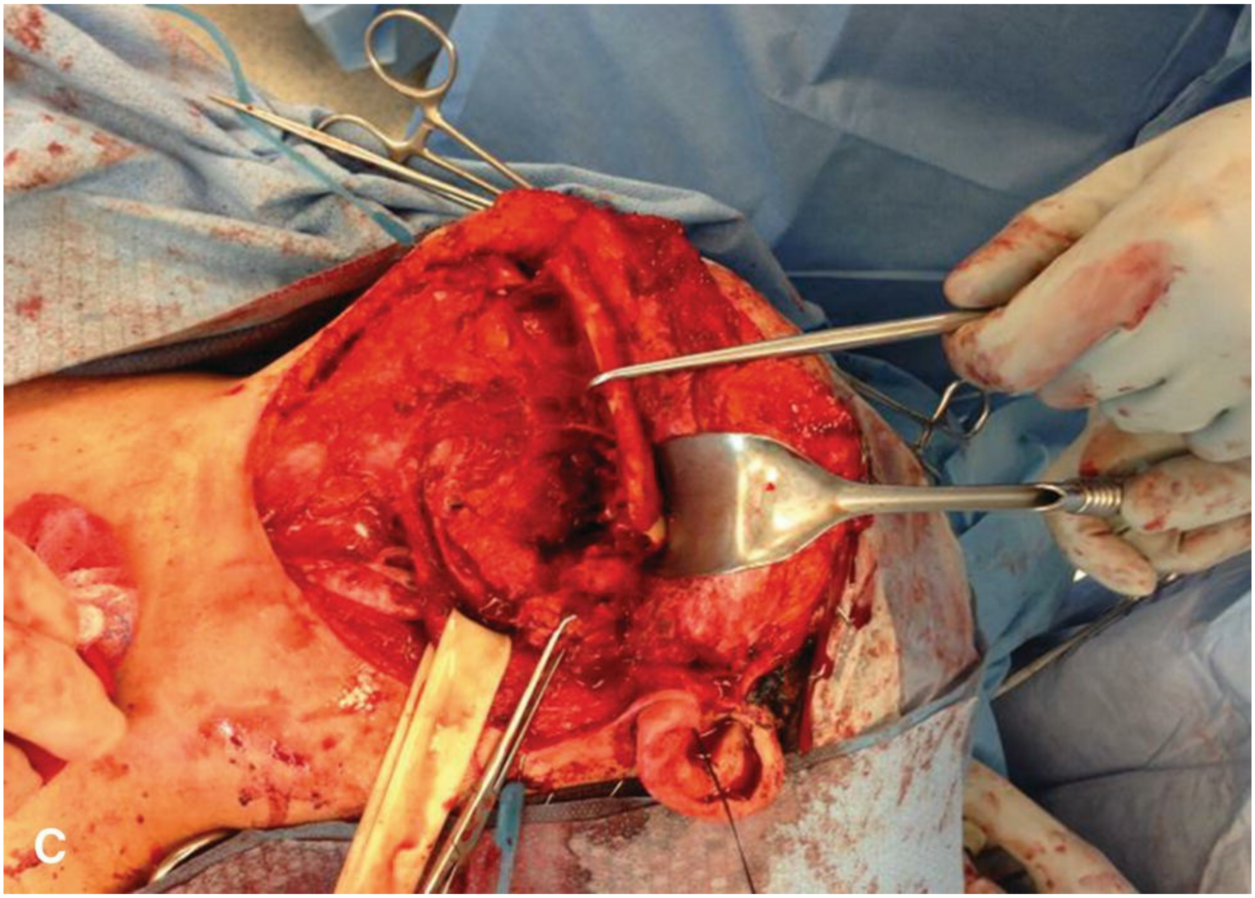
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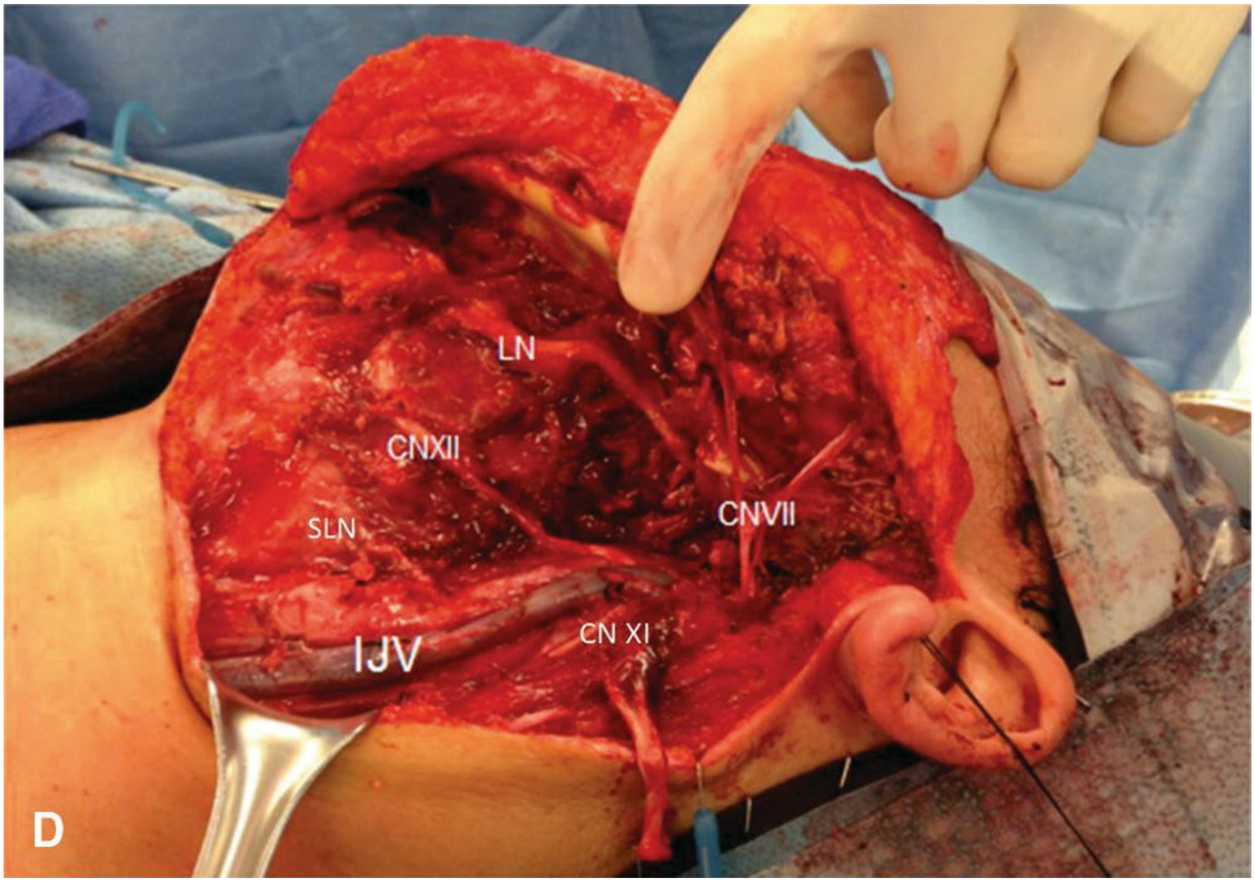
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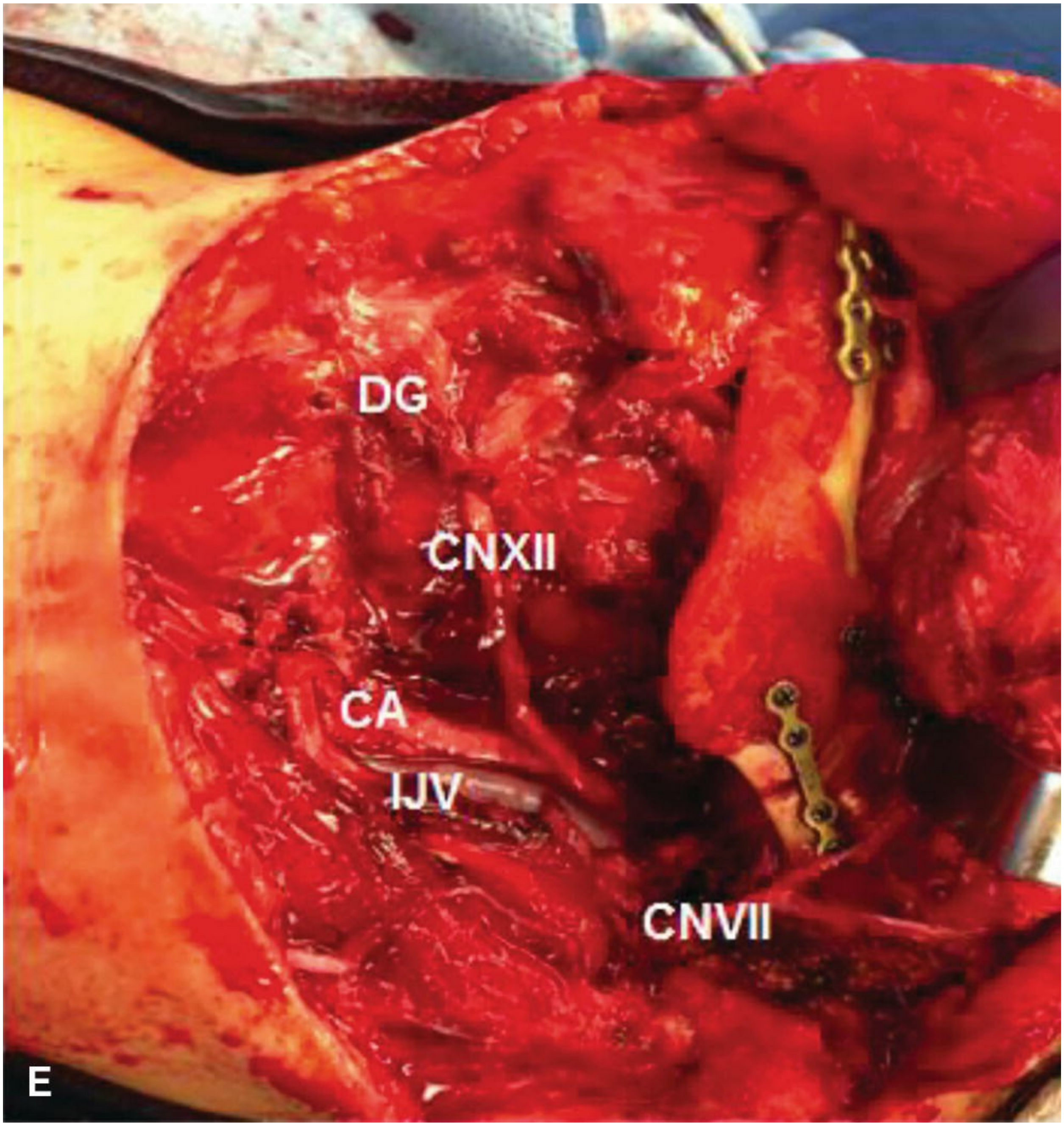

Figure 22.19. Combined transcervical–transparotid approach with mandibulotomy for excision of recurrent multifocal pleomorphic adenoma in the PPS and neck. **A** and **B**: MRI showing large irregular, infiltrative T2 hyperintense mass extending to the skull base. **C:** Mandibular osteotomies enable access to and dissection of the superior limit of the tumor. **D**: Surgical defect following total parotidectomy and neck dissection; note preservation of facial nerve branches. **E:** Reconstruction of mandible with plating system. *IJV*, internal jugular vein; *CA*, carotid artery; *CNXII*, hypoglossal nerve;

CNVII, facial nerve; *CN XI*, spinal accessory nerve; *SLN*, superior laryngeal nerve; *LN*, lingual nerve; *DG*, cut edge of digastric muscle.

Mandibulotomy Approach

The benefits of mandibulotomy to improve visualization of larger tumors in close proximity to the skull base, malignant tumors, recurrent tumors, and vascular tumors have to be balanced against the risks of malocclusion, temporomandibular joint dysfunction, inferior alveolar nerve damage, and infrequent need for tracheostomy. Regardless, patients with larger PPS tumors should always be counseled on the possibility of mandibulotomy and tracheotomy if necessary for complete tumor resection. The use of mandibulotomy in the resection of PPS tumors varies between 10% and 30% in a number of large case series.[10,11,50] A number of mandibulotomy approaches that preserve the integrity of the inferior alveolar nerve have recently been described. Jungehuelsing et al.[51] performed a single vertical osteotomy technique perpendicular to the mandibular symphysis through an intraoral approach by floor of mouth mucosal incisions. Smith et al.[52] carried out a transcervical vertical subsigmoid osteotomy posterior to the lingula, thus sparing the inferior alveolar nerve and a second mandibular osteotomy anterior to the mental foramen between the canine and first premolar teeth. Kolokythas et al.[53] utilized either a single paramedian osteotomy between the canine and first premolar alone or in combination with a horizontal osteotomy above the lingula. Prior to any osteotomies, it is essential that reconstruction plates be adapted to the contour of the native mandible through predrilled holes to ensure an accurate reconstruction during closure, thus preventing malocclusion.

Transoral Approaches

Transoral approaches for resection of PPS tumors have traditionally not been viewed favorably due to the risks of tumor rupture, incomplete tumor resection, and major neurovascular injury secondary to poor visualization.[54,55] Ducic et al.[56] in 2006 reported en bloc resection of eight nonsalivary benign tumors in the superomedial compartment of the PPS through a transoral approach with no tumor rupture. The authors used an incision extending from the posterior edge of the hard palate passing along

the lateral margin of the soft palate into the nasopharynx. Early identification and proximal and distal control of the ICA was obtained prior to tumor dissection. Combined transoral and transcervical approaches are advantageous in the resection of tumors requiring partial resection of the pharynx. In tumors that have previously undergone intraoral incisional biopsy (often ill-advised), a cuff of mucosa surrounding the site of previous incisional biopsy is incorporated in the resection of the main tumor specimen to reduce the risk of tumor spillage and subsequent multifocal recurrence within the PPS (Fig. 22.20).


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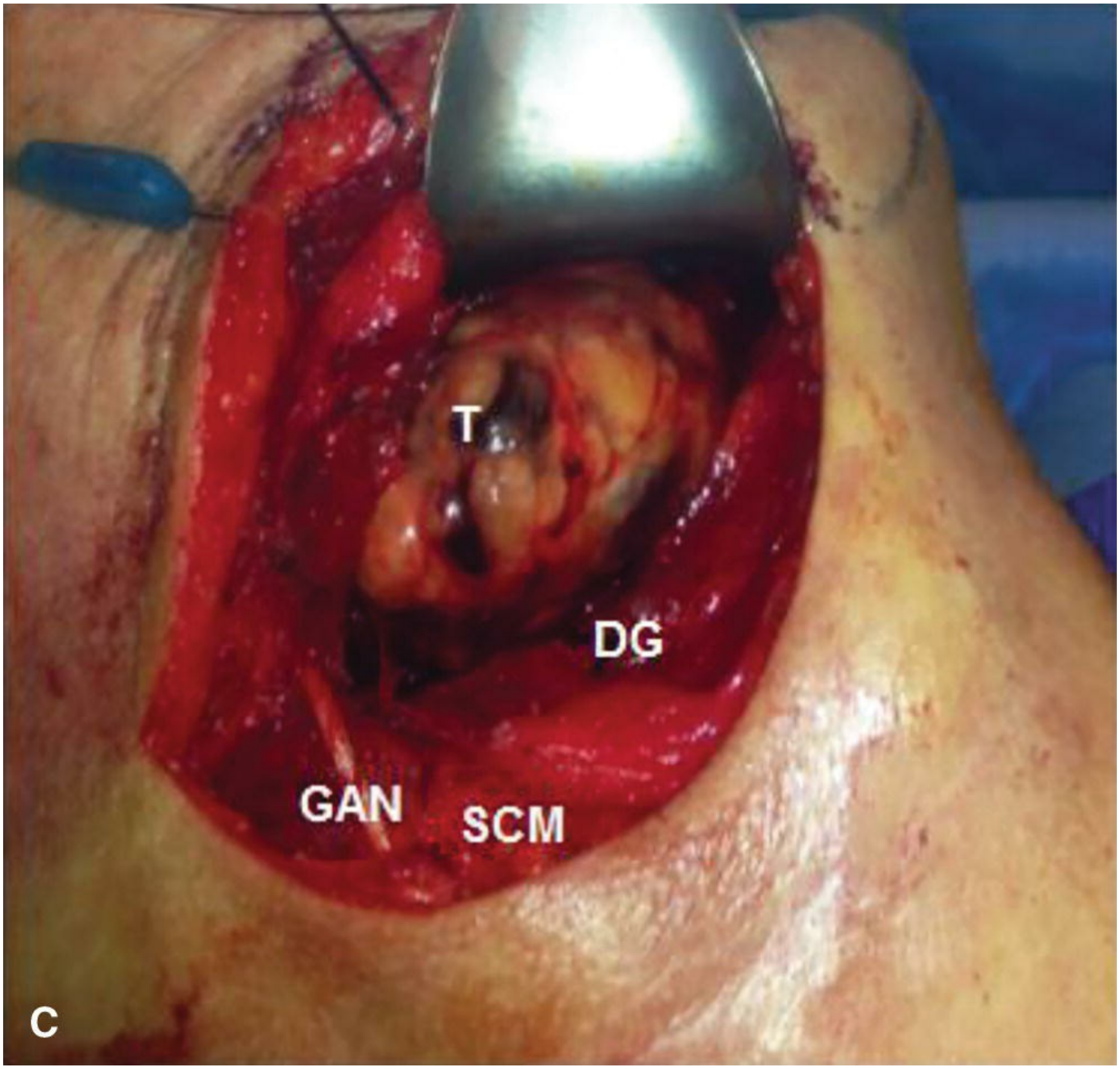
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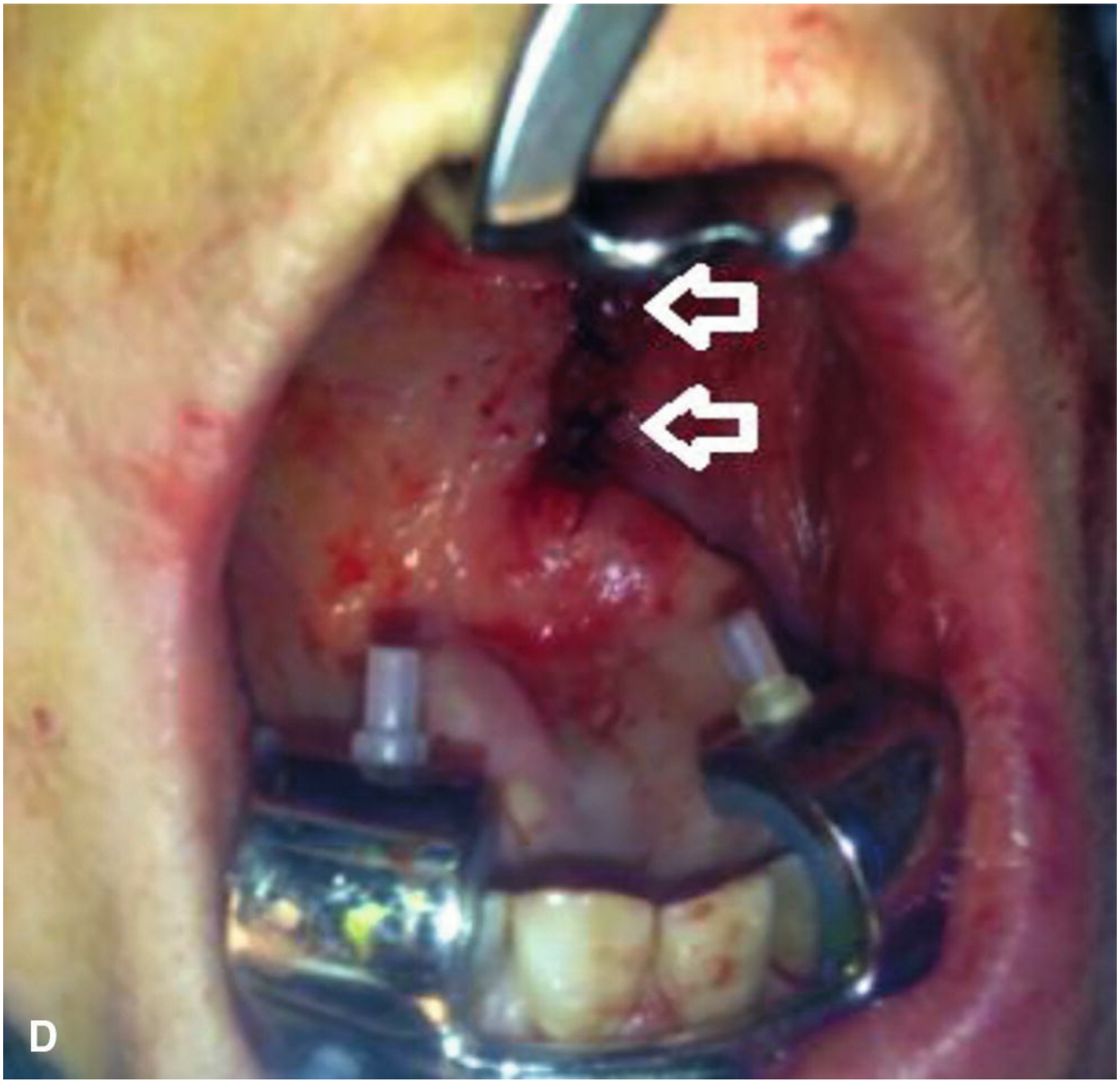

Figure 22.20. Combined transoral and transcervical approach for resection of a deep lobe pleomorphic adenoma that was previously biopsied transorally. (**A**) Coronal and (**B**) axial T2-weighted MRI of a deep lobe pleomorphic adenoma showing a heterogenous hyperintense appearance. **C**: Transcervical approach for exposure of the cervical component of the tumor (*T*), great auricular nerve (GAN), sternocleidomastoid muscle (SCM), and digastric muscle (DG). **D:** Primary repair of palate and pharynx mucosa following excision of a cuff of mucosa in continuity with tumor at previous biopsy site, *arrows* marking suture line.

Newer developments to enhance visualization during dissection of the

PPS have included the use of endoscopic techniques and transoral robotic surgery (TORS).[57,58] TORS provides a magnified, three-dimensional high-resolution view using angled scopes, greater range of movement with robot arms, and lack of a transcervical scar. There has been growing enthusiasm for resection of PPS neoplasms through a TORS approach. Chan et al.[59] recently performed a literature review of 44 patients and reported unintended tumor capsule violation or tumor fragmentation in 24% of patients undergoing TORS resection for pleomorphic adenomas. The authors question if the approach is truly “minimally invasive.” Disadvantages include the need for an incision through the superior constrictor and soft palate muscles, the inability to safely grasp the tumor capsule with sharp robotic instrumentation, lack of haptic feedback, limited space to manipulate the tumor, awkward angulation as dissection proceeds laterally deep into the PPS, and lack of carotid artery protection. Caution must be exercised using this technology, especially for pleomorphic adenomas, as the rupture rate is unacceptably high.

MANAGEMENT OF SURGICAL COMPLICATIONS

Cranial nerve injuries involving CN IX, CN X, and CN XII during resection of PPS tumors can result in speech and swallowing difficulties. CN X paralysis following resection of either a vagus nerve schwannoma or a paraganglioma should be anticipated and requires careful management to minimize morbidity. Immediate vocal fold medialization at the time of operation can assist in improving voice quality and reducing aspiration. Speech and language pathologists should be engaged to provide assessment of swallowing function and institution of swallowing therapy if required. If poor postoperative swallowing function is anticipated, alternative means of providing nutritional support via a nasogastric tube or percutaneous endoscopic gastrostomy tube should be considered. CN XI injuries incur weakness of the sternocleidomastoid and trapezius muscles and potential long-term adhesive capsulitis of the shoulder joint. Patients should receive postoperative physical therapy for range of motion shoulder exercises to rehabilitate trapezius muscle function if postoperative weakness is detected. Complete transection of CN VII results in impaired eye closure and increases

the risks of exposure keratopathy and corneal ulceration that warrants an aggressive regimen of eye lubrication with artificial tears and ointment. The most commonly used surgical strategies for treatment of lagophthalmos resulting from CN VII injury include placement of eyelid weight, canthoplasty, and canthopexy, although a whole host of other dynamic and static treatment options exist, which are beyond the scope of this chapter.

Mandibulotomies incur the risk of malocclusion, nonunion, tooth loss, and temporomandibular joint dysfunction. The risk of impaired bony union across osteotomy sites is increased with the use of adjuvant radiation. Proper attention to alignment of osteotomy segments during plating and placement of osteotomies in between tooth roots reduces these complications.

A particular complication related to resection of PPS tumors include first bite syndrome, manifested as recurrent severe pain in the parotid region with initial oral intake that subsides with subsequent chewing. Dissection within the PPS, deep lobe parotid resection, and sympathetic chain sacrifice have been shown to be strong independent risk factors for the development of this syndrome.[60] Denervation supersensitivity of the myoepithelial cell receptors following sympathetic denervation of the parotid gland has been proposed as the pathophysiology underlying this syndrome.[61,62] Severe pain related to first bite syndrome has been treated with gabapentin, pregabalin, or transcutaneous injection with botulinum toxin.[61–64] Ptosis, miosis, and anhidrosis constituting Horner syndrome can occur following disruption of the cervical sympathetic chain during surgical dissection. Velopharyngeal dysfunction following vagal injury can be ameliorated by the use of palatal prosthesis or a palatal adhesion procedure.[65]

CONCLUSION

The optimal evaluation and management of PPS tumors require a multidisciplinary team approach. A comprehensive history and physical examination allow for identification of familial tumors that may warrant further genetic counseling. An appreciation of the anatomical features of this space combined with knowledge on the commonly occurring tumors allows for accurate interpretation of radiologic imaging and treatment planning. The treatment approach of PPS tumors should take into consideration existing patient comorbidities and anticipated sequelae of surgical intervention

allowing for an informed discourse with patients on the risks, benefits, and alternatives of surgical excision. In patients who choose to undergo surgical excision, understanding of the anatomical features of this space is once again a key component allowing for maximization of intraoperative access while concurrently minimizing the risks of intervention.

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23 Ear and Temporal Bone Cancer

Paul W. Gidley

The external ear is a relatively common location for skin cancers. The external ears are susceptible to sun exposure accounting for the relatively high rate of skin cancer occurrence. Squamous cell carcinoma (SCC) of the outer ear is notorious for a relatively high metastatic rate and a higher death rate than other cutaneous sites.

Whereas the anatomic location of the ears makes them susceptible to sun-related skin cancers, the temporal bone is rarely the site of primary malignancy. Untreated external ear and periauricular skin cancers, on the other hand, can invade into the ear canal, mastoid, or stylomastoid region. Furthermore, tumors of the parotid gland, temporomandibular joint, and infratemporal fossa also erode into the ear canal and middle ear and can require a temporal bone approach for management. This chapter will present an overview of ear and temporal bone cancers.

INCIDENCE

External Ear

In the United States, approximately one million persons develop cutaneous malignancies every year.[1] The incidence of nonmelanoma skin cancer is highest in Australia with an annual occurrence of 1,200/100,000 population.[2] In a population-based study, SCC occurred on the ear as the site of first cancer in 12/100,000 men and 0.6/100,000 women.[3] The mortality rate of nonmelanoma skin cancer has been calculated to roughly 0.44/100,000.[4]

Generally speaking, external ear cancers occur in older, Caucasian men usually in their sixth and seventh decades of life.[5–9]

Cutaneous SCC is up to 17 times more common in men than in

women[10–12]. Whereas SCC of the outer ear makes up somewhere between 11% and 25% of skin cancer in men, SCC of the outer ear is found in only 0.2% to 3% of women.[3,10,13] Differences in occupation and the female style of wearing long hair may be protective.[14]

Right and left sides are equally affected, with only minor differences seen in individual studies. In comparing the incidence of left to right, these differences range from 62% to 38% to 47% to 53%.[11,15–18] Bilateral disease is found in around 10% of patients.[17] Nearly 18% of patients develop either multiple lesions or bilateral lesions during their clinical course.[8]

Temporal Bone

Primary tumors that affect the temporal bone are rare and account for only about 0.2% of all head and neck cancers.[19] Primary ear canal cancers or middle ear cancers occur at an estimated rate of one person per million people per year.[20–22] It is estimated that cancer is the underlying cause in only one in every 5,000 to 20,000 patients with an otologic complaint.[23] The temporal bone is more likely to be affected secondarily from advanced cancers of the external ear, periauricular skin, or the parotid gland (**Fig. 23.1**).[24,25]

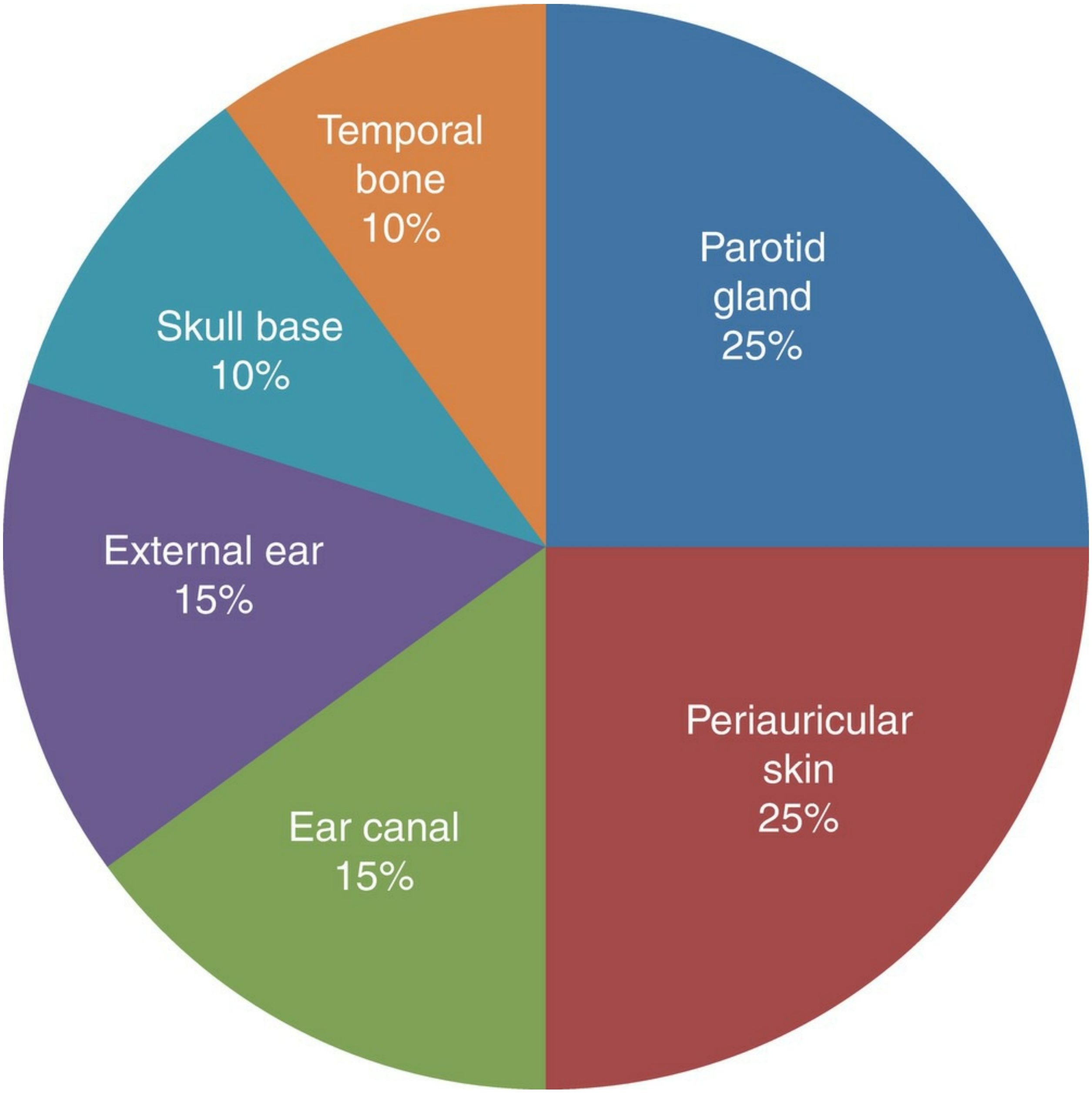


Figure 23.1. Pie chart representation of location of temporal bone primary tumors. (Used with permission, Department of Head and Neck Surgery, MD Anderson Cancer Center.)

Tumors affecting the temporal bone can occur in all age groups but typically occur in older patients, especially in men. In a large series of temporal bone cancers, 75% of patients were men, and the average age was 65 years.[26] The tumor histologies tend to trend with age, so that younger patients are likely to have sarcomas and older patients are likely to have carcinomas.

ETIOLOGY

Overwhelmingly, the leading cause of external ear cancer is ultraviolet solar radiation.[27] In the sun-drenched parts of the United States, cancer of the external ears is a common clinical entity. The prominent location of the external ear makes it vulnerable to sun exposure. Radiotherapy has also been implicated as a risk factor for development of SCC. According to Conley and Schuller,[28] SCC is also found in patients with burn chondritis and chronic scarring lupus erythematosus.[29]

Radiotherapy has been linked with squamous cell cancer of the middle ear and ear canal.[30–32] Some authors have linked chronic otitis media and cholesteatoma to ear canal and middle ear cancer,[30,33–36] but this etiology probably accounts for only a small number of tumors in most modern studies. HPV16 has been found in only a small number of temporal bone SCCs.[37]

HISTOLOGIC TYPES

External Ear

Basal and squamous cell carcinoma are far and away the most common malignancies to affect the outer ear and its surrounding skin.[12] The outer ear is estimated to make up 5% to 10% of all skin cancers.[9,38,39] For the head and neck, the external ear is the second most common site of cutaneous SCC.[10] In the subset of patients with metastatic spread of cutaneous SCC in the head and neck, the outer ear accounts for 20% of the primary sites; and this rate is higher than for lip (15%) or cheek (12%) primary sites.[40]

Although basal cell carcinoma (BCC) is almost four times more common than SCC as a cutaneous malignancy in other body sites,[41–43] an analysis limited to the outer ear found that their incidence is nearly equal (1.3 BCC:1 SCC).[14] In another study of 780 patients with external ear cancer, SCC was found to affect 55% of patients.[5] In reviewing the literature, SCC made up 55% to 67% of malignancies affecting the outer ear, whereas BCC made up 28% to 32% and melanoma was 1% to 5%.[17]

Unlike most cutaneous SCCs, which have a low rate of metastatic spread

to regional lymph nodes (range 0.5% to 5%),[6,44–46] SCC from the ear has a much higher rate, ranging from 10% to 16%.[7,8,15,47]

Overall, when compared to other cutaneous sites, SCC from the auricle has the highest death rate, nearly 47% in one study.[4] It has been estimated that cancers originating from the ear are responsible for more than 25% of deaths caused by nongenital, nonmelanoma skin cancers.[48]

Given all the features and facts listed above, the ear is considered a high-risk area for BCC and SCC as documented in the latest National Comprehensive Cancer Network (NCCN) guidelines[49,50] and AJCC staging.[51]

Melanoma of the external ear is a unique disease in its own right. The external ear is involved relatively infrequently with melanoma. In the United States, roughly 1% of the 48,000 new cases of melanoma involve the outer ear.[52] While approximately 20% of melanomas occur in the head and neck[53], the external ear accounts for approximately 7% to 15% of melanoma cases in head and neck sites.[53,54] Of the four subtypes of melanoma described, superficial spread and nodular melanoma are the most common to be found on the external ear.[54] For melanoma of the external ear, the rate of metastatic spread to regional lymph nodes is very high. Byers et al.[54] noted an overall incidence of clinically positive nodes in 42 of 102 patients. The presence of metastatic neck disease was found to be a significant correlate for survival.[54]

A recent review of the incidence of external ear cancers seen at the University of Texas MD Anderson Cancer Center is listed in **Table 23.1**. In our patient population, BCC was slightly more common than SCC and its variants. Our patient cohort has nearly as many malignant melanoma patients as SCC probably owing to the fact of our location in the southern US Sunbelt and due to referral bias as a comprehensive cancer institution.

Table 23.1 Histologic Types of External Ear Cancers at University of Texas MD Anderson Cancer Center Between 1990 and 2006

Cancer Type	No. of Patients	%
Basal cell carcinoma	527	30.1%
Basosquamous carcinoma	70	4.0%
Squamous cell carcinoma	388	22.2%
Squamous cell carcinoma in situ	41	2.3%
Squamous cell carcinoma, adenoid variant	25	1.4%
Squamous cell carcinoma, spindle cell variant	5	0.3%
Carcinoma in situ, Bowen disease	8	0.5%
Melanoma, malignant	386	22.1%
Melanoma arising in melanotic freckle	64	3.7%
Melanoma in situ	22	1.3%
Malignant neoplasm unclassifiable	158	9.0%
Carcinoma, NOS	20	1.1%
Merkel cell carcinoma	15	0.9%
Atypical fibrous histiocytoma	6	0.3%
Angiosarcoma	3	0.2%
Unusual tumors[a]	10	0.6%
	1,748	100.0%

[a]Unusual tumors occurring in two or fewer patients during this time include adnexal carcinoma (1), apocrine carcinoma (1), adenocarcinoma (1), adenoid cystic carcinoma (1), papillary squamous carcinoma (1), sarcomatoid carcinoma (1), sebaceous gland carcinoma (1), atypical fibroxanthoma (2), and angiomatoid fibrous histiocytoma (1).Used with permission, © Paul Gidley, MD 2009.

Temporal Bone

Perhaps as a result of its location in the lateral skull base, the temporal bone is affected by a long list of tumor types (**Table 23.2**).[26] Squamous cell and BCC account for more than 50% of the tumors if all primary tumor sites are considered. When primary locations outside the temporal bone are excluded, SCC accounts for 60% to 80% of the tumors that arise in the ear canal, middle ear, or mastoid cavity.[55–57] BCC and adenoid cystic carcinomas (ACCs) are the next two most common tumors found in the ear canal.[58]

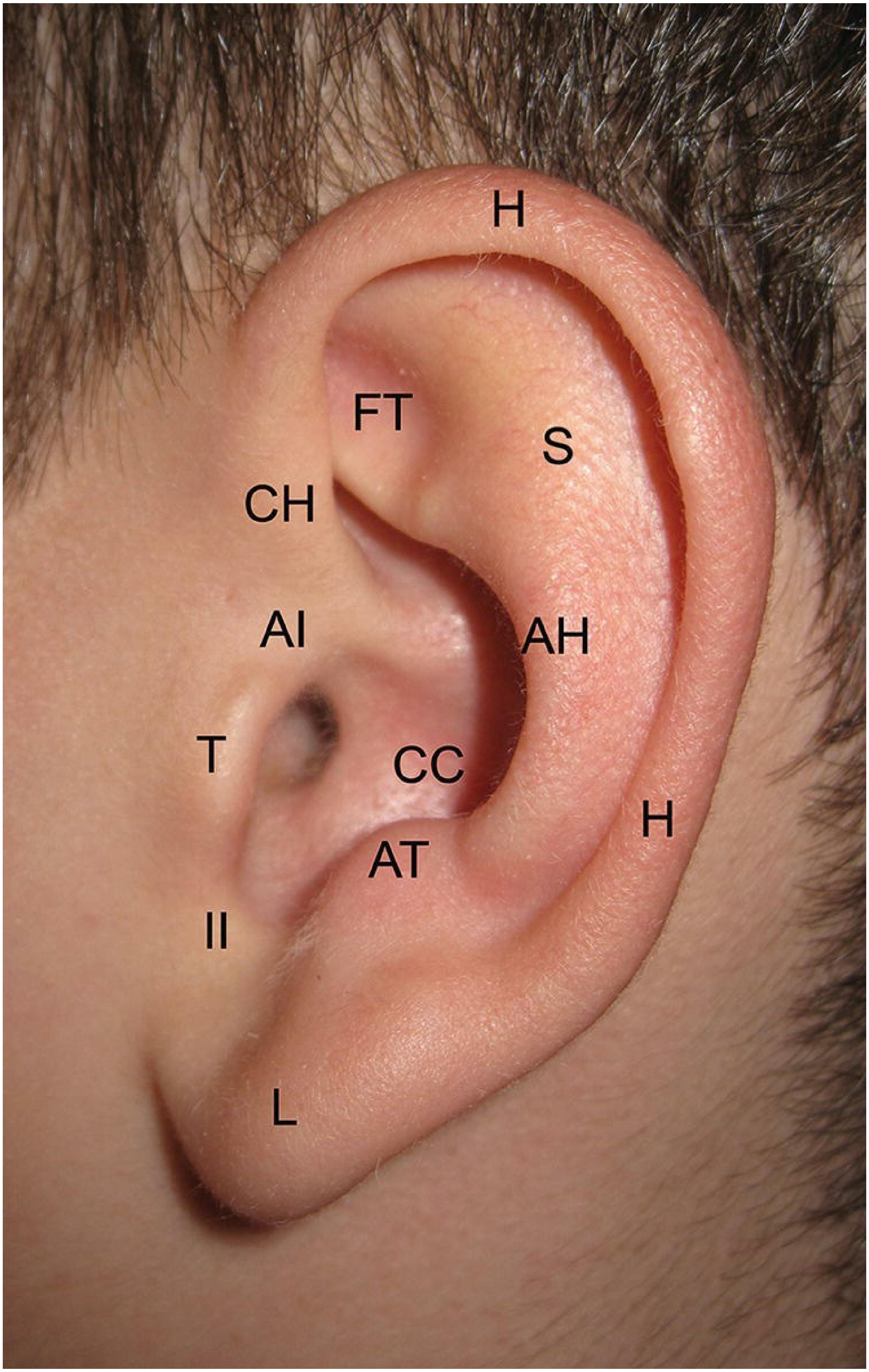
Table 23.2 List of Malignant Tumor Types Found Affecting the Temporal Bone

Epithelial
Squamous cell carcinoma
Basal cell carcinoma
Adenoid cystic carcinoma
Basosquamous carcinoma
Hidradenocarcinoma
Melanoma
Sarcomatoid carcinoma
Sebaceous cell carcinoma
Sarcomas
Chondrosarcoma
Osteosarcoma
Pleomorphic sarcoma
Spindle cell sarcoma
Salivary
Adenoid cystic carcinoma
Acinic cell carcinoma
Adenocarcinoma
Basal cell adenocarcinoma
Carcinoma ex pleomorphic adenoma
Malignant mixed carcinoma
Mucoepidermoid carcinoma
Salivary ductal carcinoma
Other
Clivus chordomas
Hemangiopericytoma
Neuroendocrine carcinoma
Peripheral nerve sheath tumor

ANATOMY

Embryologically, the auricle arises from the six hillocks of His. These hillocks each give rise to one or more of the structures of the outer ear. The area in front of the ear, at the sideburn in men, marks an area of embryologic fusion plane.[59] These fusion planes are thought to play a role in the depth of invasion of tumors and perhaps contribute to the insidious and profound invasion that is a notorious hallmark for this anatomic site.[5] Equally, the embryologic compartments from each hillock might explain why tumor spread is limited in the early stages of the disease.[59]

Anatomically, the outer ear can be described by its parts: helix, antihelix, tragus, antitragus, lobule, concha, and scapha (**Fig. 23.2**).[60] The conchal bowl can be further subdivided into a concha cavum and a concha cymba. The scapha is divided by branching of the antihelix, thus creating a fossa triangularis. The ear stands out from the scalp creating a posterior, or sometimes called medial, surface.


H
FT
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L

Figure 23.2. Anatomic subdivision of the external ear. (AH, antihelix; AI, anterior incisura; AT, antitragus; CC, conchal cavum; CH, crus of helix; FT, fossa triangularis; H, helix; II, intertragic incisures; L, lobule; S, scaphoid fossa; T, tragus.) (From Gidley PW. Special considerations: periauricular lesions. In: Weber RS, Moore BA, eds. *Cutaneous Malignancy of the Head and Neck: A Multidisciplinary Approach*. San Diego, CA: Plural Publishing, Inc.; 2011:155–172, with permission.)

The skin of the anterior surface of the pinna is tightly bound to the underlying perichondrium and cartilage, whereas the skin of the posterior surface is thicker and has more soft tissue between the skin and the perichondrium. The lymphatics are in the space between the skin and perichondrium. The relatively high incidence of metastatic spread in external ear cancers might be explained by the short vertical distance between the epidermis and the lymphatics, and this anatomic fact may account for the high incidence of neck metastasis from both SCC and melanoma despite their different cells of origin.[61]

The helix is the most common site of auricular carcinomas, accounting for approximately 50% of tumors.[8,11] This observation is true across the three major histologic types (**Table 23.3**). The concha and scapha account for approximately 17% to 30% of tumors.[8,16,17] The posterior surface is involved in 12% to 28% of tumors (**Fig. 23.3**).[8,62,63] The lobule is involved in 2.7% to 8% of tumors.[8]

Table 23.3 Sites of External Ear Involvement from Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC), and Melanoma

Anatomic site	Bailin[59] BCC	Afzelius[15] SCC	Byers[8] SCC	Shockley[16] SCC	Silapunt[18] SCC	Byers[54] Melanoma	Cole[65] Melanoma
Helix	58%	51%	53%	44%	50.7%	58.8%	47%
Antihelix and triangular fossa	18.6%	15%	19%	14%	17.4%	0%	0%
Posterior pinna	18.6%	27%	14%	27%	16%	0%	11%
Lobule	2.3%	1.5%	5%	6%	6.2%	23.5%	21%
Concha	4.7%	4.5%	5%	6%	7.6%	5.9%	5%
Tragus	0%	0%	4%	3%	1.4%	11.8%	5%

NS, not stated. Used with permission, © Paul W. Gidley, 2009.

Figure 23.3. BCC involving the posterior surface of the pinna. (From Gidley PW. Special considerations: periauricular lesions. In: Weber RS, Moore BA, eds. *Cutaneous Malignancy of the Head and Neck: A Multidisciplinary Approach*. San Diego, CA: Plural Publishing, Inc.; 2011:155–172, with permission.)

One study of melanoma of the external ear described that centrally located tumors (concha, tragus, and antitragus) have a worse prognosis than do more peripherally positioned tumors.[64] Interestingly, the triangular fossa and antihelix were not reported as involved by melanoma in two large series.[54,65]

The external auditory meatus has two parts: a lateral cartilaginous part, which has a relatively thick epidermis with hair follicles, and a medial bony part, which has a relatively thin epidermis devoid of hair follicles. The bony–cartilaginous junction marks an important landmark when evaluating external ear canal lesions. Lesions that involve the bony canal will require lateral

temporal bone resection (LTBR) for complete extirpation, whereas lesions that are confined to the membranous canal can often be resected with only soft tissue.

The tympanic membrane (TM) marks another important landmark in evaluating external ear canal tumors. Tumors that are lateral to the TM can usually be completely excised with LTBR, whereas tumors that involve the middle ear, mastoid, facial nerve, and deeper structures will require more extensive surgical resection. Once a tumor fills the ear canal, physical examination becomes less useful, and CT and MRI are necessary to determine the extent of disease.

SIGNS AND SYMPTOMS

The physical examination of these patients demands close scrutiny of the external ear, ear canals, tympanic membranes, parotid gland, periauricular skin, cervical lymph nodes, and cranial nerves. Microscopic examination of the ear canal is important to determine the extent of disease into the ear canal.

External Ear

External ear cancers usually present as a nonhealing ulcer. Itching and occasional bleeding are other common symptoms (**Fig. 23.4A**). Far advanced and neglected tumors can erode away skin and reveal the cartilaginous framework (Fig. 23.4B and C). Facial paralysis and facial numbness are ominous signs of perineural spread.


A


B

Figure 23.4. A: Early-stage external ear BCC. **B:** Advanced BCC eroding external ear and exposing cartilage. **C:** Neglected SCC involving the outer ear; only a small portion of the helix is still visible. (Used with permission, University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery.)

Temporal Bone

The signs and symptoms of these tumors are vague and can be confused with benign disease. Otorrhea, otalgia, and hearing loss are the most common symptoms of temporal bone tumors.[66] However, these symptoms are also seen in benign conditions such as otitis externa, otitis media, or cholesteatoma.[67] The majority of patients with benign disease will respond to aural toilet and eardrops or oral medications. Suspicion should arise when patients with these symptoms do not respond to standard therapy.[67]

The classic triad of otorrhea, otalgia, and hearing loss is found in only 10% of temporal bone cancer patients. If patients with these symptoms do not respond to standard therapy, then any suspicious tissue should be sent for pathologic evaluation.

The differential diagnosis for disease in the ear canal should include skull base osteomyelitis (also called malignant otitis externa), pseudoepitheliomatous hyperplasia, and carcinoma.[68] The diagnosis unfortunately is delayed in many patients, and the duration of symptoms can vary from months to several years. [66,69]

Other symptoms, such as trismus, facial weakness, dysphagia, and hoarseness, are seen much less commonly and are usually associated with advanced-stage disease. The temporal bone and ear canal are a rare location for metastatic lesions, usually from breast, lung, prostate, or kidney primaries.[70–73]

SCC involving the ear canal will have an exophytic or ulcerated appearance (**Fig. 23.5**) and can be heralded by erythematous skin and granulation tissue. BCC usually has an ulcerated appearance with rolled edges. ACC in its early stage is often subcutaneous (**Fig. 23.6**). Occasionally, some tumors will have a subcutaneous spread and a cursory examination of the canal might miss the ear canal involvement (**Fig. 23.7**).

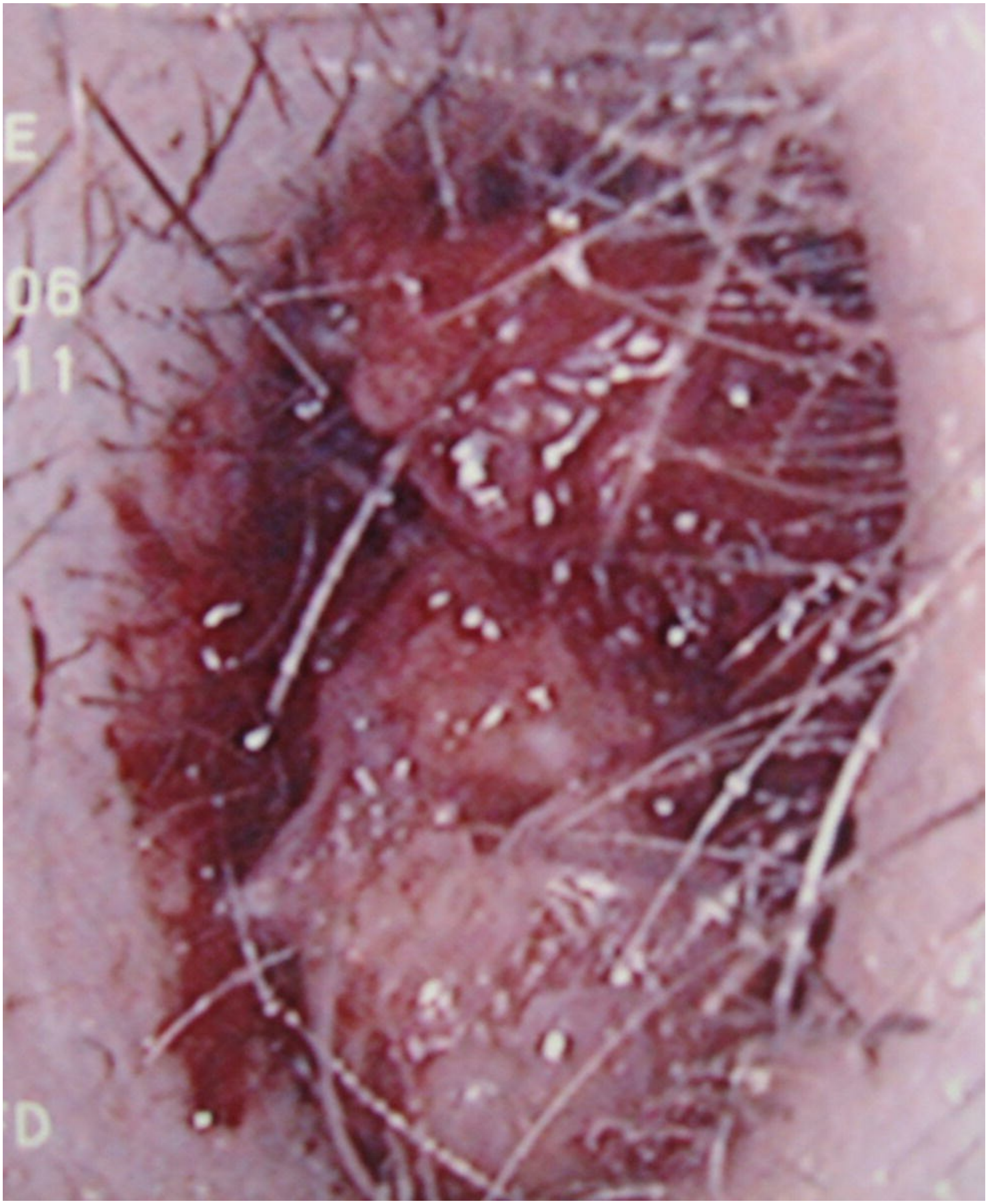


Figure 23.5. SCC filling the left ear canal. (Used with permission, Department of Head and Neck Surgery, University of Texas MD Anderson Cancer Center.)

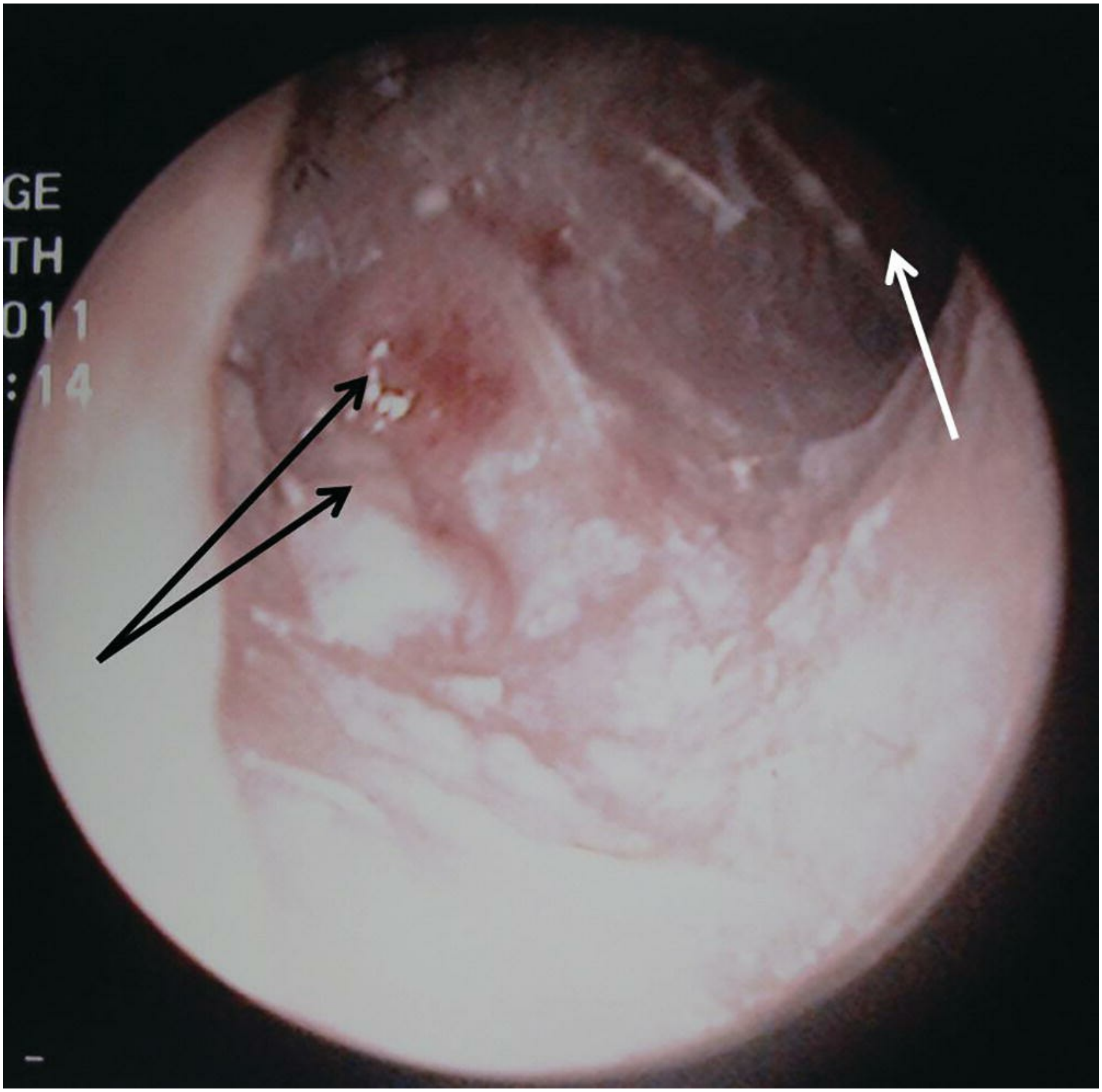


Figure 23.6. Small ACC of the external auditory canal, showing subcutaneous and ulcerated disease (*black arrows*). Tympanic membrane (*white arrow*). (Used with permission, University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery.)

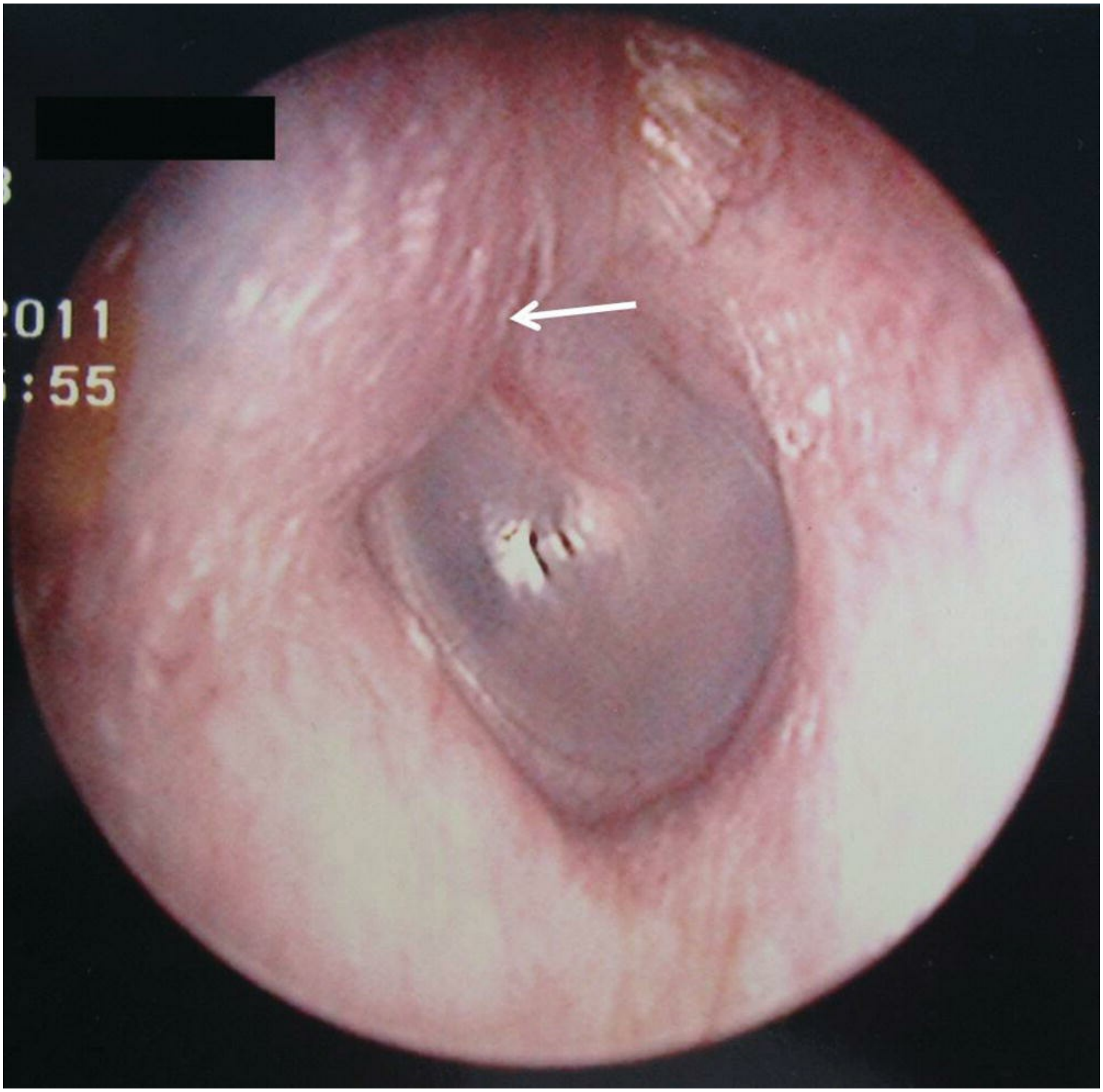


Figure 23.7. Subtle left anterosuperior ear canal swelling (*arrow*) due to infratemporal fossa chondrosarcomas. (Used with permission, Department of Head and Neck Surgery, University of Texas MD Anderson Cancer Center.)

Facial paralysis, when it occurs, is a very ominous finding. It's linked with a poor prognosis.[25,74,75] In a series from MD Anderson, approximately 40% of patients had various degrees of facial weakness or paralysis at presentation.[26] Cervical lymphadenopathy is a particularly poor prognostic sign associated with worse survival.

DIAGNOSTIC IMAGING

Small, early-stage external ear cancers usually do not require any imaging studies; however, late-stage skin cancers, tumors that have spread to parotid gland or lymph nodes, or tumors that involve the ear canal demand radiographic evaluation. Diagnostic imaging is imperative for understanding the three-dimensional anatomy of external canal and temporal bone tumors. CT scan and MRI provide complementary details.[76] CT scan is generally obtained as an initial study because it gives an excellent view of soft tissue and bony anatomy.[77] Given that MRI lacks bony detail, its use is reserved as an adjunct especially in cases where dural involvement or perineural invasion is suspected (**Fig. 23.8**).

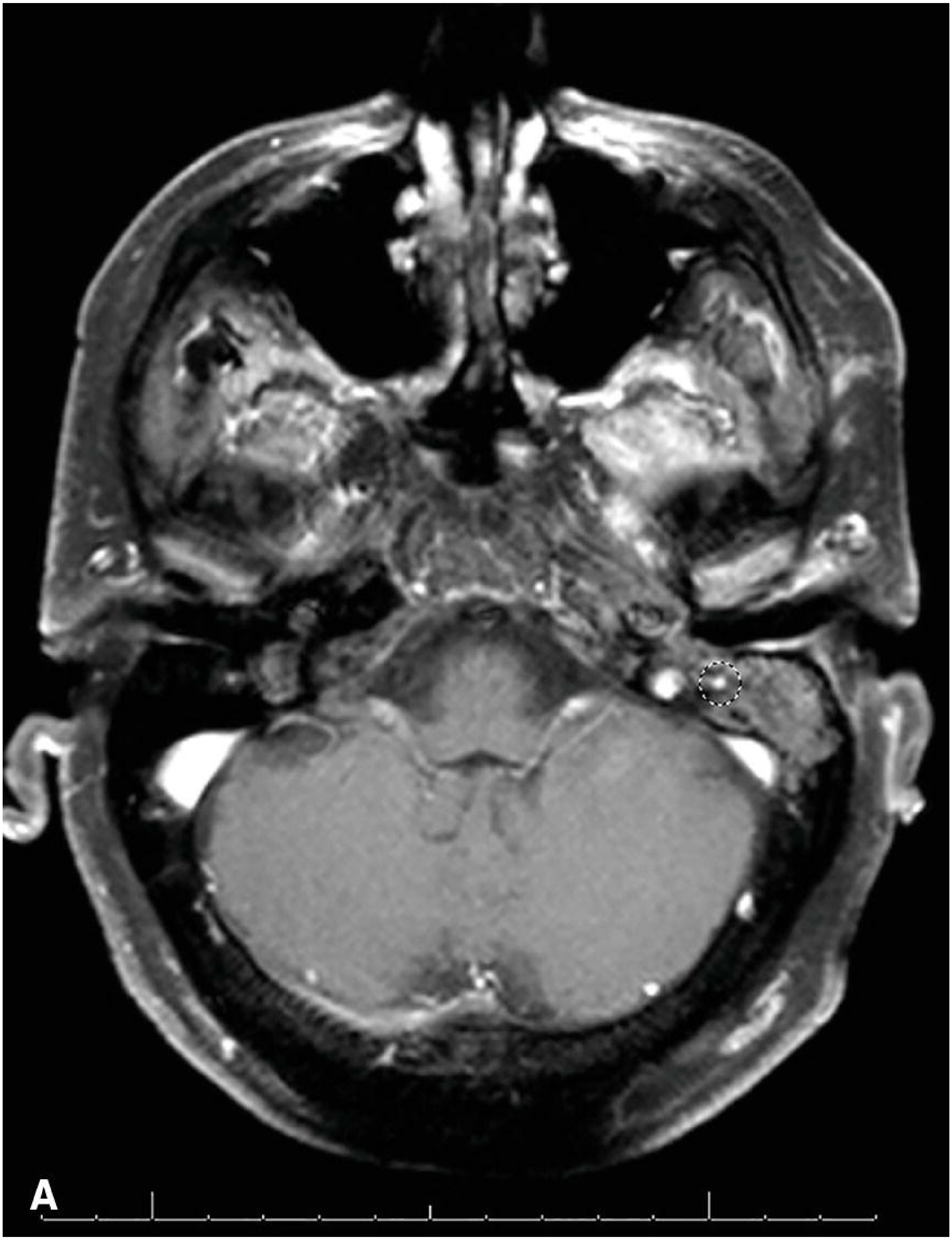

A

Figure 23.8. Perineural spread along the left facial and trigeminal nerves from an ear canal SCC. **A:** Axial MRI showing enhancement of the mastoid portion of the left facial nerve (*circled*). **B:** Axial CT showing enhancement of the left trigeminal nerve as it enters Meckel cave (*arrow*). (Used with permission, University of Texas MD Anderson Cancer Center, Department of

Head and Neck Surgery.)

CT and MRI can be reviewed systematically by noting disease involvement at 12 important sites: the 4 quadrants of the ear canal, the infratemporal fossa, middle ear, otic capsule, mastoid, jugular foramen, carotid canal, tegmen or middle fossa and posterior fossa.[78]

Leonetti and colleagues[79] looked at different paths of invasion of temporal bone tumors. They identified that tumors grow superiorly through the tegmen, anteriorly through the glenoid fossa and infratemporal space, inferiorly through the hypotympanum and jugular foramen, posteriorly into the mastoid, and medially through the carotid canal and inner ear. They noted that anterior and inferior spread is accurately assessed by CT scan and MRI; however, they found that there was underestimation of disease when disease involved mastoid and middle ear mucosa, the tegmen tympani, the middle fossa dural, or the carotid canal. Local recurrences were found in these four areas on retrospective review.[79]

STAGING

External Ear

The staging of cutaneous carcinomas (excluding carcinoma of the eyelid and melanomas) has been updated, and this marks a departure from previous staging schemes. Although the external ear does not have a unique staging system, it is considered a high-risk factor in the 2010 AJCC TNM staging for cutaneous malignancy (**Table 23.4**).[51] This staging system takes into account the high-risk features of depth of invasion, perineural invasion, and histologic differentiation. Two centimeters (2 cm) continues to be an important demarcation for staging. An external ear cancer with two or more high-risk features is considered T2 regardless of size. An external ear cancer that invades the temporal bone is considered T3. Perineural invasion of the skull base (e.g., facial or trigeminal nerve) is considered T4.

Table 23.4 TNM Staging for Cutaneous Carcinomas

Primary Tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension with <2 high-risk features[a]
T2	Tumor >2 cm in greatest dimension OR Tumor any size with ≥2 high-risk features[a]
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton or perineural invasion of skull base
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension
N2b	Metastases in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
N2c	Metastases in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
N3	Metastasis in a lymph node, >6 cm in greatest dimension
Distant Metastasis (M)	
M0	No distant metastases
M1	Distant metastases

[a]High-risk features for T stage: (1) depth/invasion >2 mm thickness (Breslow thickness), Clark level ≥ IV, or positive perineural invasion, (2) poorly differentiated or undifferentiated, or (3) anatomic location of the ear.Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Temporal Bone

There is not an AJCC-approved staging system for temporal bone cancers. Several staging systems have been proposed.[22,80–83] The first iteration of the University of Pittsburgh Staging System was proposed by Arriaga and colleagues[81] in 1990 and was modified more recently by Moody and colleagues[19] (**Table 23.5**). This staging system provides a comprehensive means of assessing these tumors, and the Pittsburgh T stage has been shown to predict overall survival.[25,66,75] The presence of facial paralysis is an important change in the current system of staging when compared to the original iteration.[84]

Table 23.5 Modified Pittsburgh Staging System[19] for Squamous Cell Carcinoma of the Temporal Bone

T Classification	Description
T1	Limited to the EAC without bony erosion or evidence of soft tissue involvement
T2	Limited to the EAC with bone erosion (not full thickness) or limited soft tissue involvement (<0.5 cm)
T3	Erosion through the osseous EAC (full thickness) with limited soft tissue involvement (<0.5 cm) or tumor involvement in the middle ear and/or mastoid
T4	Erosion of the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen, or dura; with extensive soft tissue involvement (>0.5 cm, such as involvement of the TMJ or styloid process); or evidence of facial paresis
N Classification	
N0	No regional nodes involved
N1	Single metastatic regional node <3 cm in size
N2	
N2a	Single ipsilateral metastatic node 3–6 cm in size
N2b	Multiple ipsilateral metastatic lymph nodes
N2c	Contralateral metastatic lymph node
N3	Metastatic lymph node >6 cm in size
Overall Stage	
I	T1N0
II	T2N0
III	T3N0
IV	T4N0 and T1-4N+

EAC, external auditory canal; TMJ, temporomandibular joint; N+, any positive lymph node.

Given that cervical lymphadenopathy carries a poor prognosis, overall staging for temporal bone tumors is slightly different than staging for other head and neck tumor sites. T1N0 tumors are stage 1, T2N0 tumors are stage 2, and T3N0 tumors are stage 3. However, stage 4 tumors include T4N0 and any T with N+ status.[81]

RISK FACTORS FOR NODAL METASTASIS IN EXTERNAL EAR CANCERS

Many authors have struggled to identify risk factors for nodal metastasis in order to determine which patients will need parotidectomy and/or elective neck dissection:

- Location on or around the external ear as an independent risk factor for metastatic spread.[9,15,85,86] The metastasis rate for the external ear was 11.0% versus 5.2% for sun-exposed skin.[86]
- Horizontal size.[85–88] TNM staging uses 2 cm to separate T1 from T2 lesions. The NCCN guidelines consider any ear tumor ≥6 mm in size to be a high-risk lesion for recurrence and metastasis.[50]
- Tumor thickness, more than 4 mm.[40,85,86,89] In a prospective study of 615 patients with cutaneous SCC, nodal metastasis occurred in 4% of patients with tumors 2.1 to 6.0 mm in thickness and in 6% of patients with tumors thicker than 6.0 mm.[85] Another study of 509 patients found that a tumor thickness of 5 mm is an important determinant of lymph node metastasis. Nodal metastasis was found in 2.9% of patients with lesion thickness ≤5 mm and was 17.5% when tumor thickness was >5 mm. Their mean follow-up was 5.3 years.[90]
- Depth of invasion. Tumors that reach Clark level V had a metastatic rate of 30.6%, whereas tumors that reach Clark level IV had only a 10% rate.[15] A more recent study found that patients with nodal metastasis were significantly more likely to have invasion beyond Clark III.[88] Furthermore, invasion beyond subcutaneous tissues has been found to be an independent indicator of outcome.[87]
- Degree of differentiation.[88,90,91] SCC lesions of poor histologic differentiation have double the local recurrence rate and triple the metastatic rate of those lesion that are well differentiated.[86] Others have also been unable to make a correlation.[15,47,85]
- Immunosuppression. In the setting of organ transplantation, immunosuppression has been linked with development of nonmelanoma skin cancers, especially SCC.[85,92] Although immunosuppressed patients may only account for 5% of the cutaneous SCC population,[40] the overall risk to these patients of developing a malignancy is high. By one estimate, the chance of a patient developing one cutaneous malignancy post renal transplant is 66% within 24 years.[93] In a series of 68 organ transplant patients with metastatic skin cancer (85% SCC), the median primary size was only 12 mm, the median depth of invasion was only 3.2 mm, and the 3-year disease-specific survival was only 56%, thus indicating a lower threshold for metastatic spread and worse prognosis in this clinical setting. [94]

- Perineural invasion.[88,95–97] Perineural invasion is found in 5% to 10% of tumors and is associated with a higher incidence of nodal metastasis.[40,88,95] Goepfert et al.[96] reported a significant increase in both nodal (35% vs. 15%) and distant (15% vs. 3.3%) metastasis for patients with perineural invasion versus those without.
- Lymphovascular invasion. Lymphovascular invasion was found in 40% of patients with nodal metastasis versus 8% of patients without nodal metastasis.[98]
- Other features: cartilage or bone invasion[7,15]

INCIDENCE OF LYMPH NODE METASTASIS

External Ear

The overall incidence of lymph node metastasis from SCC is 2% to 4%.[6,46,85] Lymph node metastasis is a significant prognostic marker for any skin cancer. In the United States, 2,500 patients die annually from advanced skin cancer, usually developing metastatic lymph nodes during their clinical course.[99]

Whereas cutaneous SCC from other body areas has a low rate of metastatic spread to regional lymph nodes (range 0.5% to 2%),[44,45] SCC from the outer ear has a much higher rate, ranging from 10% to 16%.[8,15,47,63] In a meta-analysis, the incidence of lymph node metastasis to the parotid and upper cervical chain for SCC was found to be 11.2%.[61]

The rate of metastatic spread from auricular melanoma is even higher, perhaps as high as 40%.[100] Byers et al.[54] noted an overall incidence of clinically positive nodes in 42 of 102 patients with melanoma of the outer ear.

A systematic data review found that lymph node metastasis occurred in 85% of patients within the first 12 months and in 98% of patients within the first 24 months of diagnosis.[12,61,101]

The lymphatics of the outer ear drain to preauricular, postauricular, parotid, and upper cervical lymph nodes.[8,11,102] The parotid and upper jugular

nodes are the most frequent site of involvement.[47,54,61,102] Turner et al.[12] noted that 70% of their patients had parotid involvement, 30% had cervical node involvement, and 14% had both. The most common site of lymph node involvement is levels II and III.[12] Suboccipital nodes have not been found involved.[8]

Temporal Bone

The incidence of lymph node metastasis has been considered to be low in temporal bone cancers. This perception is probably related to the small numbers of tumors seen and the wide variety of histologic tumor types, some which are known to metastasize and others which usually do not metastasize. In a literature review examining 18 papers and covering nearly 500 patients with SCC of the ear canal and temporal bone, the mean incidence of lymph node metastasis was 17.7%.[103]

The first echelon of lymphatic drainage for SCC of the ear canal and temporal bone is to level II and to intraparotid nodes.[56,66,104]

TREATMENT—SURGERY

Surgical Margins

Consistent with all head and neck tumors, negative surgical margins are consistently associated with superior disease-free and overall survival.[105] Incompletely excised tumors are at high risk for local recurrence and neck metastasis.[86,106] The rate of incomplete excision of SCC from the external ear is higher than all other skin sites (20.5% vs. 4.8%, $p = 0.001$).[107,108] As a result, the recommendation was for an excision margin of 5 mm where feasible.

In a prospective study of BCC, Wolf and Zitelli[109] found that 4-mm margins were needed to eradicate 95% of BCC that are <2 cm in diameter. Thomas et al.,[106] using a Mohs surgical technique, recommend a 4-mm margin for nonmelanoma skin cancers up to 20 mm wide. Similar support is found for both BCC and SCC.[109]

The National Comprehensive Cancer Network of America 2014 guideline

recommends a 4- to 6-mm surgical margin for SCC.[49,50]

Margins for melanomas have also been studied. Narayan and Ariyan[110] did not observe any recurrences for patients with 1-cm negative margins. Pockaj et al.[111] reported that 80% of recurrences occurred in patients with a margin <1 cm. Most authors recommend a 1-cm margin for invasive ear melanoma.[110,112]

SURGICAL TECHNIQUES

External Ear Cancers

- Cryosurgery, curettage, and electrodesiccation[113–115]

This technique has been reported to be useful in previously untreated, nodular lesions. The tumor is electrodesiccated and removed with a curet. The curet allows the surgeon to distinguish between tumor and normal skin.[109] Recurrence rates for favorable BCCs are generally low, but repeated treatments might be required.[115] This treatment is not appropriate for tumors that are large, infiltrating, fibrosing, or recurrent. The ear has been identified as a high-risk area for recurrence when treated by electrodessication.[116]

- Mohs micrographic surgery (MMS)

For SCC, MMS has been shown to be effective in complete excision and superior in local tissue conservation.[117] In a cosmetically prominent area, such as the external ear, conservation of local tissue is important. Multiple studies have shown low recurrence rates with this technique, usually <5%.[5,18,86,118–121] Primary wound closure, split-thickness skin grafts, healing by secondary intention, and local flaps have all been described as useful in reconstructing the resulting defect.[117,122]

- Wide local excision and their reconstructions[8,47,123]

The goal of surgical excision is complete tumor removal with minimal cosmetic deformity. Because most tumors occur on the helix, simple wedge

excision with primary closure can be achieved with good cosmetic results. Tumors of the conchal bowl can be excised and the site reconstructed with a skin graft. Local flaps can be employed in reconstructing helical, scapha, conchal bowl and lobule cancers. Several articles have described these techniques.[117,123–142]

- Total auriculectomy

Total auriculectomy is needed only for tumors that occupy most of the pinna. In this circumstance, the tumor almost always extends into the ear canal, and complete excision will require an LTBR with parotidectomy and neck dissection. Leaving the ear canal intact, while excising all of the external ear cartilage, risks canal stenosis and trapping of debris, precipitating chronic otorrhea. This situation is compounded when postoperative radiotherapy (PORT) is given.

Temporal Bone Cancer

Whereas single-modality radiotherapy has been reported as treatment for temporal bone tumors,[143–145] surgical resection has been considered the standard of care.[75] Surgical management of these tumors is predicated on and tailored to the extent of disease. The goal of surgery is to extirpate disease, achieving a negative margin, while minimizing morbidity or mortality.

- Local canal excision

Small, early-staged tumors that are confined to the cartilaginous outer ear canal can be managed with a wide local excision[56]. This situation occasionally arises in the case of a tragal-based or conchal-based tumor that extends into the membranous ear canal. This procedure is usually performed under general anesthesia using the operative microscope. An endaural incision helps with visualizing tumor extent. Skin and underlying cartilage are excised using frozen section pathology for margin evaluation. Reconstruction is performed with a split-thickness skin graft.

The skin of the bony ear canal is thin and achieving a negative deep margin is difficult once the tumor reaches the bony ear canal. If the medial (or bony canal) extent of the tumor cannot be cleared, then the procedure

should be converted to an LTBR. Anecdotally, surgeons have tried to remove the skin from the bony ear canal, the so-called sleeve resection, reconstructed the defect with a split-thickness skin graft, and used radiotherapy as a salvage therapy. This situation usually develops into a narrow ear canal with exposed bone and chronic drainage and ultimately can lead to osteoradionecrosis of the temporal bone. LTBR provides better tumor control and overall survival for these patients.[58]

- Lateral Temporal Bone Resection

The real workhorse of otologic oncologic surgery is the LTBR. This procedure removes the bony canal en bloc lateral to the facial nerve. The goal of LTBR is en bloc resection of tumors involving the external auditory canal without tumor spillage. The strategy to achieve this goal is bony dissection to free the external canal. Details of this procedure have been previously published.[146] The specimen includes the tympanic membrane, malleus, and incus. The stapes, facial nerve, and inner ear structures are preserved. The amount of cartilaginous ear canal and pinna resected depends on the tumor extent in these structures. LTBR can be combined with parotidectomy, neck dissection, mandibulectomy, and craniotomy. Reconstruction technique will depend on the defect and is influenced by previous irradiation.

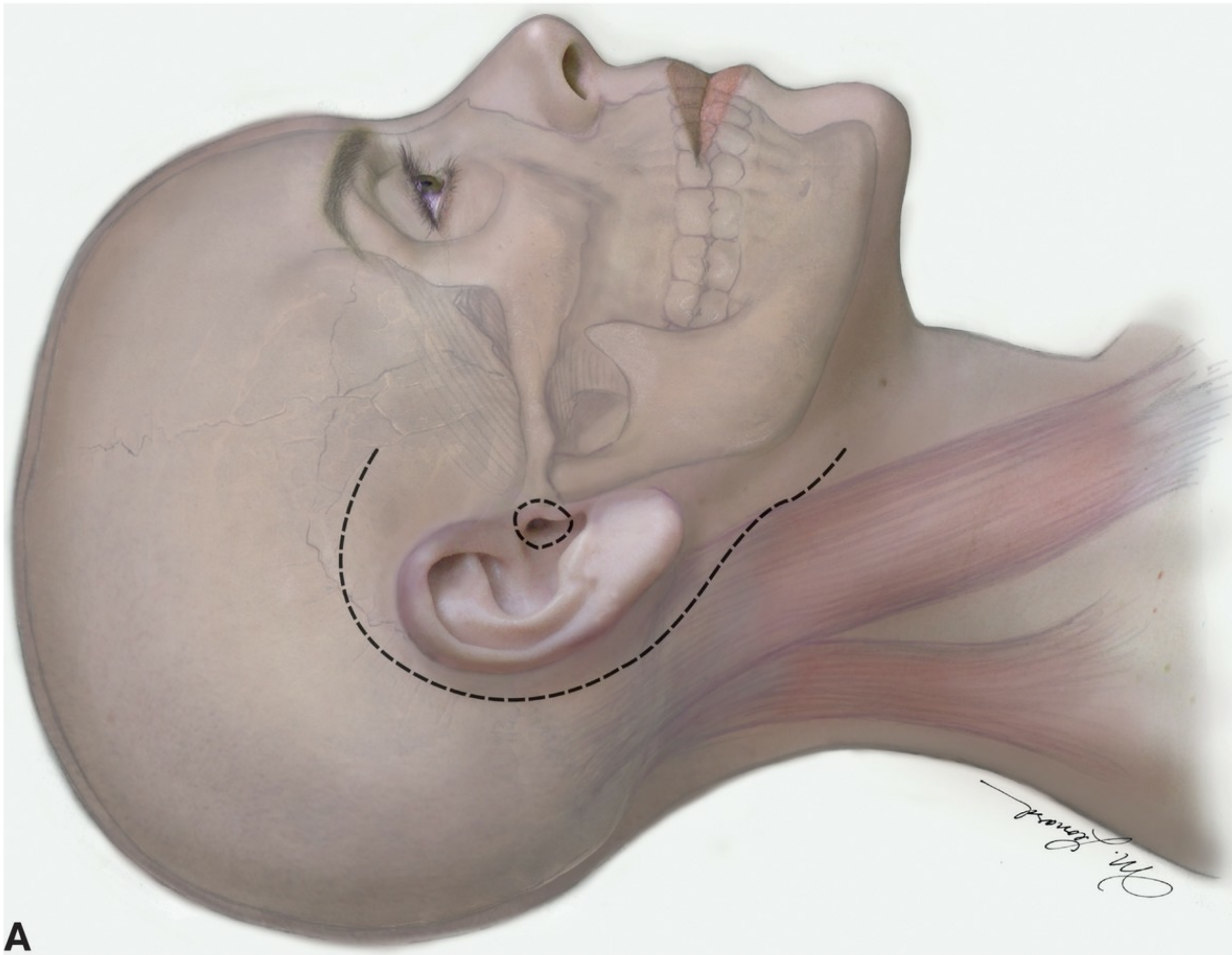
General Considerations

LTBR with parotidectomy, neck dissection, and possible microvascular free flap reconstruction usually requires 8 to 12 hours of general anesthesia. The patient’s general health must allow such a surgical procedure. Intraoperative facial nerve monitoring is always used, and this fact must be communicated to the anesthetist to avoid use of long-term paralytics. Antithromboembolism techniques, TED hose and sequential compression devices, are also used.

Skin Incision

The surgeon has a choice of incisions for temporal bone resection. This decision is based on location of tumor; the need for auriculectomy, parotidectomy, and/or neck dissection; previous incisions; and the need for craniotomy. A large postauricular C-shaped incision is perhaps the most versatile incision and is utilized when the auricle is normal (**Fig. 23.9A**).[146]

The external auditory meatus is cut lateral to the tumor. The auricle can be elevated with a wide anteriorly based skin flap. This incision gives access for parotidectomy, neck dissection, craniotomy, and temporalis muscle flap.



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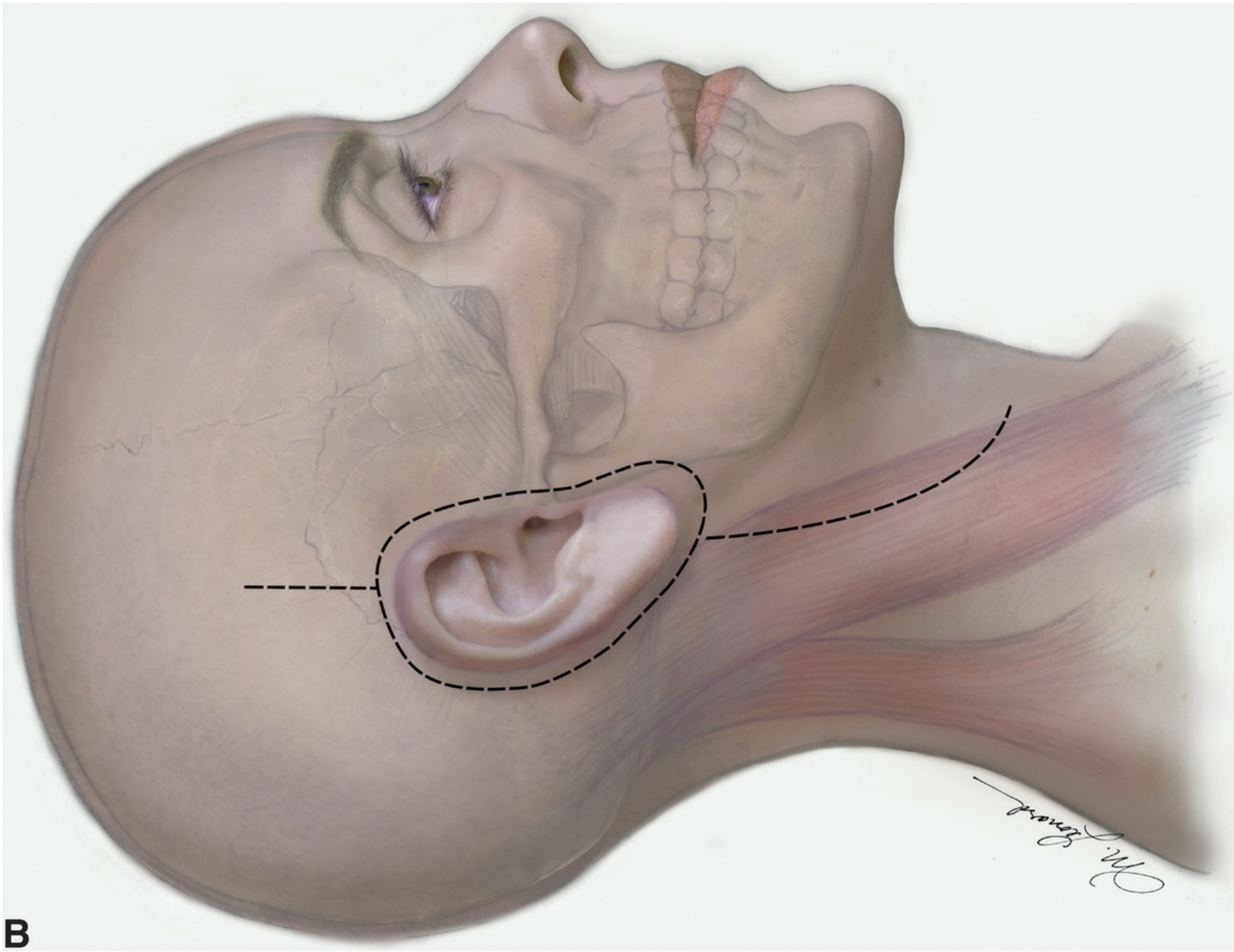

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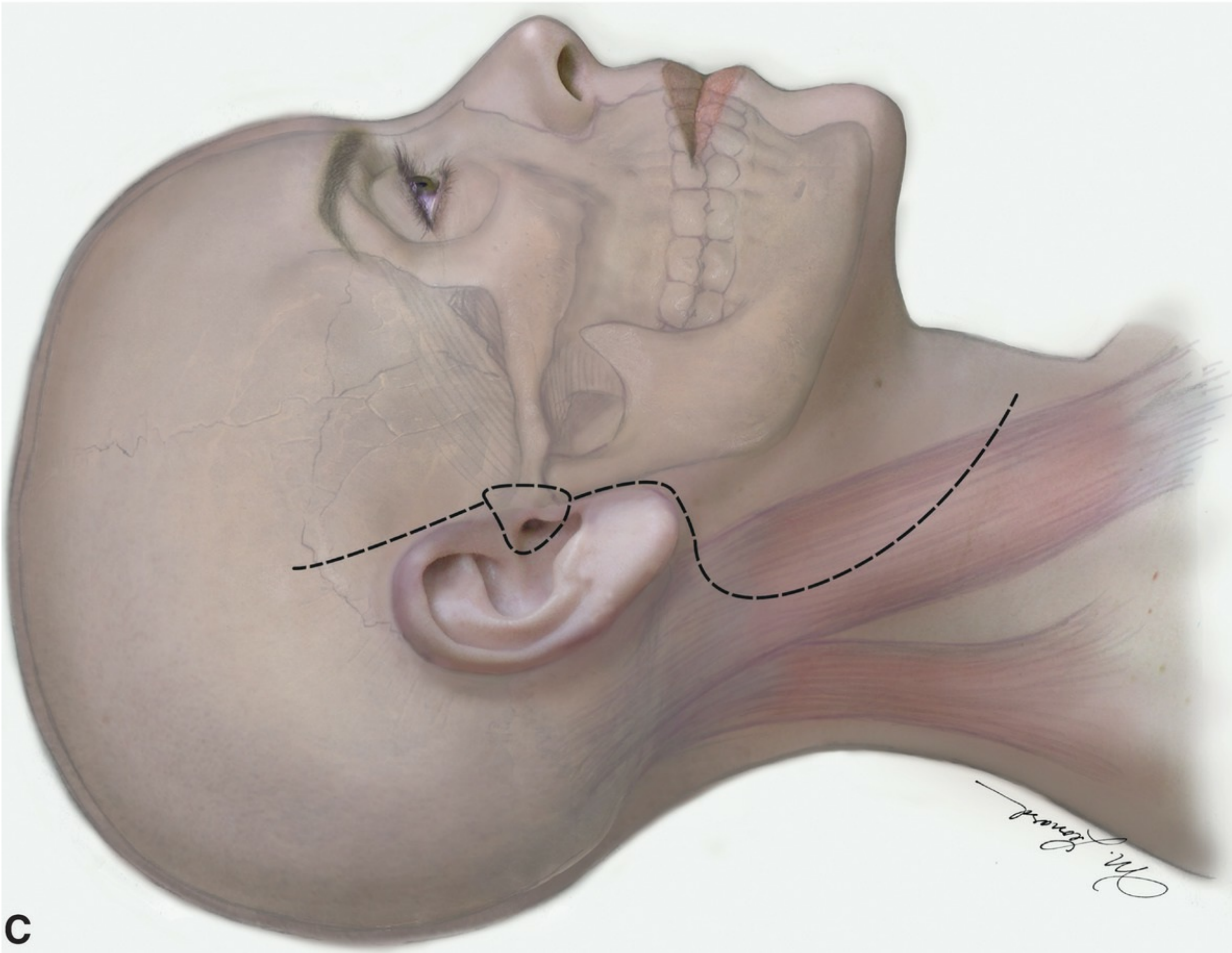


Figure 23.9. Incisions for LTBR. **A:**C-shaped postauricular incision. **B:** Total auriculectomy incision. **C:** Preauricular incision with canal ellipse. (From Gidley PW. Lateral and subtotal temporal bone resection. In: Cohen JI, Clayman GL, eds. *Atlas of Head and Neck Surgery*. Philadelphia, PA: Elsevier Saunders; 2011:438–449, with permission.)

When auriculectomy is required, an incision that circumscribes the tumor and auricle is used (Fig. 23.9B). Surrounding skin can be undermined giving enough exposure for LTBR, parotidectomy, and neck dissection. Limited middle fossa craniectomy can be performed through this approach. This situation produces the largest soft tissue defect and generally requires microvascular free flap for closure.

When the tumor is confined to the ear canal, a modified parotidectomy incision can be combined with an elliptical incision around the external meatus (Fig. 23.9C). This incision is especially advantageous in the circumstance of recurrent disease following previous parotidectomy or

radiotherapy. The incision can be extended anterior to the helix and superiorly into the temporal scalp. The remaining pinna is elevated with a broad posteriorly based skin flap. This incision is probably best for T1 and T2 ear canal cancers and parotid-based tumors that involve the ear canal. Parotidectomy and neck dissection are performed, and reconstruction can be with either a temporalis muscle flap or microvascular free flap. The posteriorly based skin flap containing the pinna has some disadvantages: (1) the pinna is folded or retracted, which could compromise its blood supply and (2) the temporal bone surgeon has to work over the flap containing the pinna.

Bony Dissection

Following skin incisions, a complete mastoidectomy is performed. The tegmen is thinned and used as a guide to judge the level of the middle fossa dura. The antrum is opened, the attic is widened, and the incus and malleus head are identified. The horizontal semicircular canal is preserved throughout this dissection.

Bone at the root of the zygoma is removed, and the temporomandibular joint is identified at its lateral bony margin. Drilling continues through zygomatic air cells, working between the bony ear canal and tegmen and staying lateral to the ossicular chain. Care is taken to avoid a dural tear and to avoid violating the external ear canal bone and spilling tumor into the operative field. The entire TMJ capsule is exposed from medial to lateral.

The facial recess is opened, and the middle ear is checked for disease. (If disease is found in the middle ear, the surgical procedure will need to expand beyond an LTBR.) The facial nerve is identified at its tympanic segment and followed through its mastoid course to the stylomastoid foramen. The digastric ridge is drilled away to identify the underlying digastric muscle. A cut is made in the anterior wall of the mastoid tip, lateral to the facial nerve and inferior to the tympanic ring. This maneuver liberates the mastoid tip, and its soft tissue attachments are cut with electrocautery. Removal of the mastoid tip unifies the mastoid with the neck, and it allows the facial nerve to be traced from the mastoid into the parotid gland.

The facial recess is then extended and the chorda tympani nerve is divided. The annulus is identified, and drilling continues between the annulus and the facial nerve until the hypotympanum is reached. The inferior

tympanic bone is removed, and the soft tissue anterior to the tympanic ring is identified. In making the inferior final cut, care must be exercised to avoid having the shaft of the drill rest on the facial nerve. Only prudent surgical technique can avoid injury to the facial nerve here, because the facial nerve monitor will not alarm from thermal injury to the nerve.

The final bony cuts are made to free the anterior-inferior extent of the tympanic ring. Occasionally, the carotid artery is in contact with the annulus here. Vigilance is required to avoid injury to a laterally placed carotid artery.

The incus is disarticulated. Thumb pressure on the canal causes it to fracture anteriorly. A Freer elevator can be used to assure that the canal is entirely mobilized, but care must be taken to avoid using the facial canal or middle fossa dura as a fulcrum.

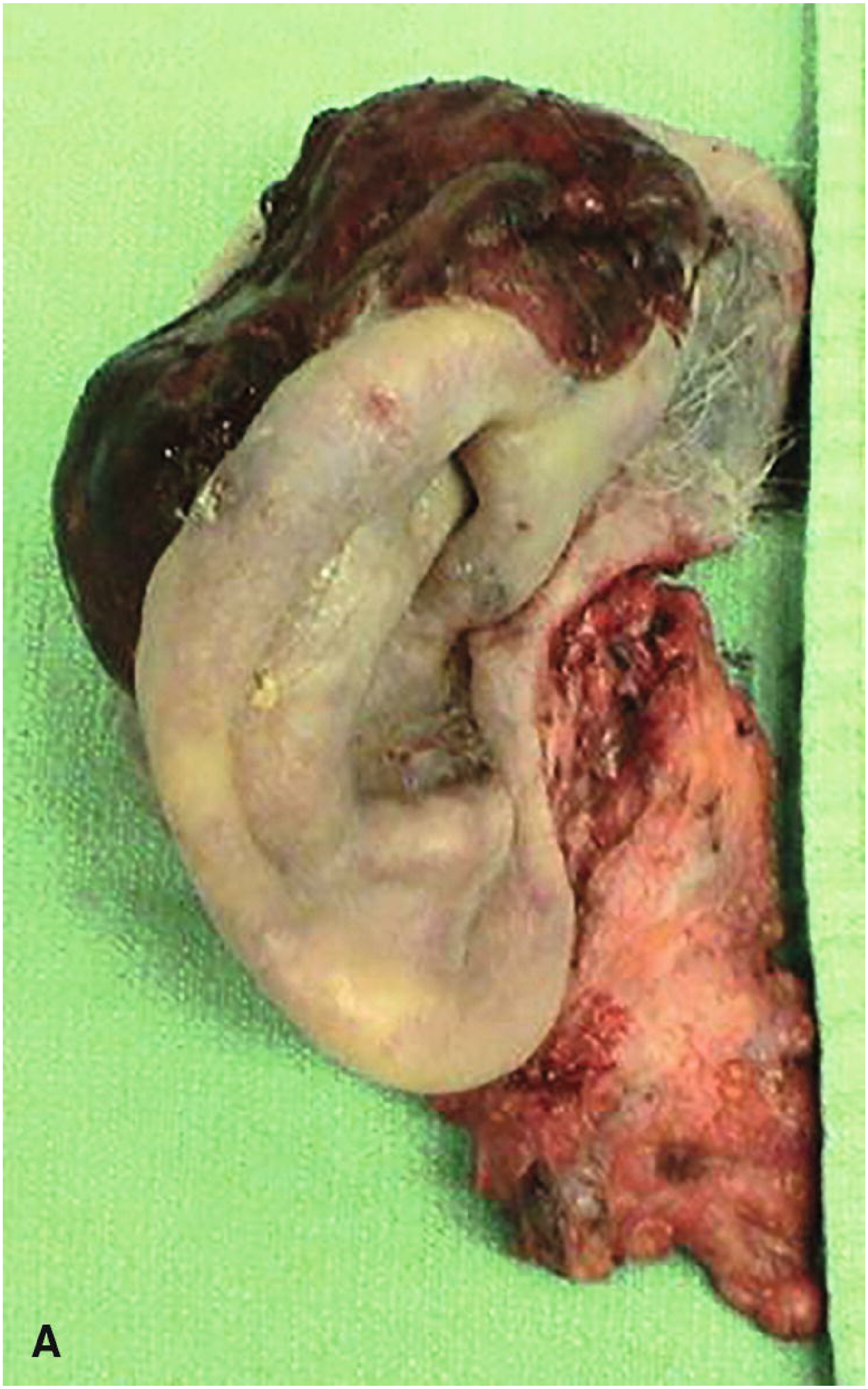
Facial Nerve Management

The mastoid segment of the facial nerve can be decompressed, and the nerve traced into the parotid gland to aid in parotidectomy. The facial nerve can be assessed for perineural disease. Perineural disease can produce a nerve that is thicker and redder than usual. If the patient has normal facial function preoperatively, then efforts should be made to preserve this function. If the patient has pre-existing facial paralysis and facial nerve sacrifice is planned, then the nerve can be divided and the proximal end sent for frozen section evaluation. A tumor-free margin should be sought; however, a labyrinthectomy is not performed for the sole reason of trying to achieve a negative facial nerve margin. Our philosophy has been to treat this remaining microscopic disease with PORT. Successful facial nerve grafting and reasonable survival can be achieved even when microscopic disease remains in the proximal segment of the facial nerve.[147]

If nerve sacrifice is required and if usable proximal and distal segments are available, then an attempt should be made at facial nerve grafting.[148,149] The great auricular nerve is a reasonable choice for short defects; however, the facial nerve defects that result from LTBR and parotidectomy are usually too long to be grafted with the great auricular nerve. The cutaneous branch of the anterior femoral nerve, which is in the field of the anterior lateral thigh flap, and the sural nerve are better options.[148]

Some tumors can be adequately treated with LTBR alone; however, the

majority of cases will require concomitant parotidectomy and upper neck dissection (levels II and III). These procedures commence following LTBR. Large auricular cancers and large parotid tumors can be resected en bloc along with the ear canal. This surgery creates a “composite resection” that includes the external ear, ear canal, parotid, and neck dissection and occasionally the upper mandible as one single specimen (**Fig. 23.10**).



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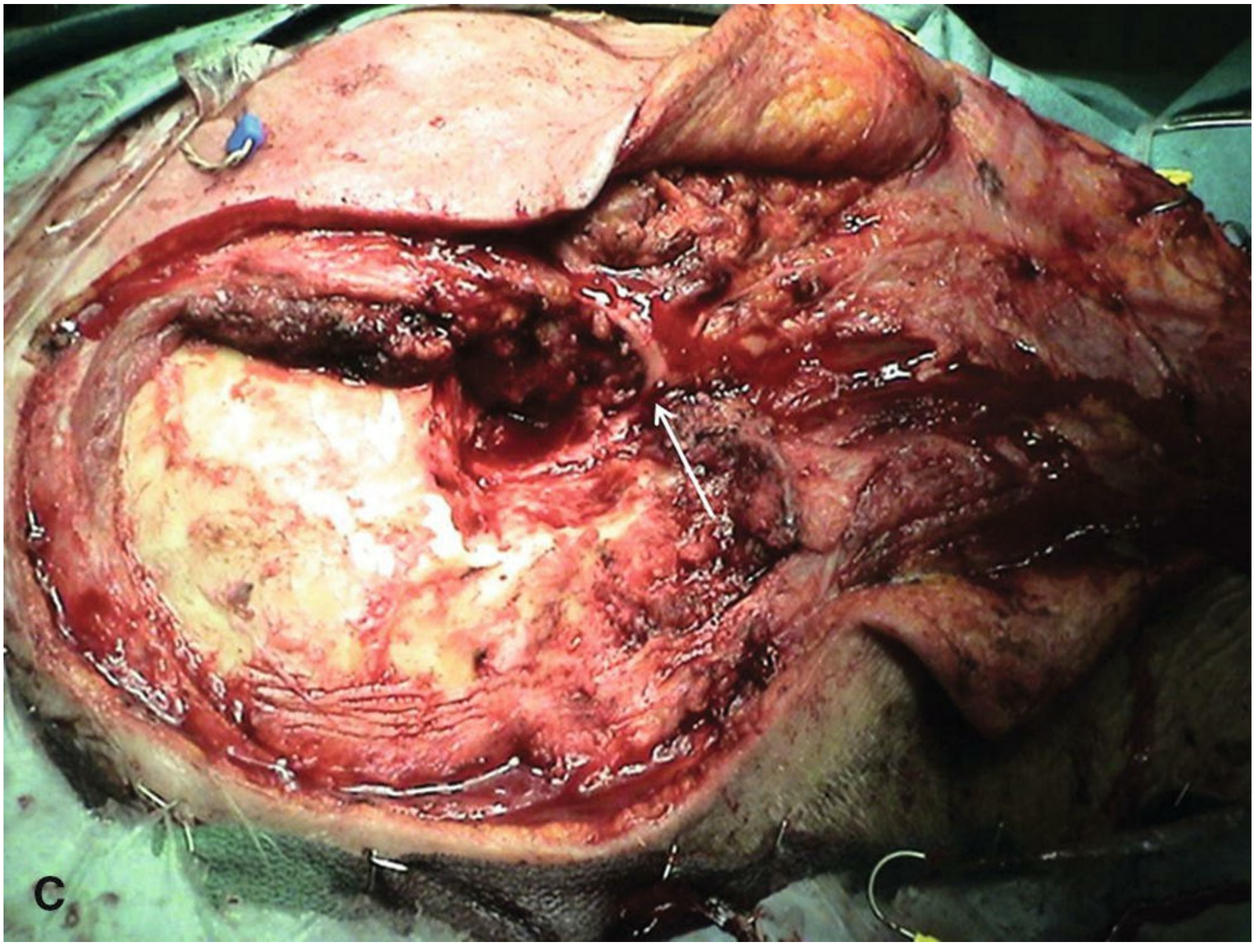

Figure 23.10. A: Large auricular cancer removed as a composite resection including auricle, ear canal, parotid, and neck dissection. **B:** Undersurface of defect shows intact ear canal and TM. **C:** Defect shows intact facial nerve (*white arrow*) and was reconstructed with an anterior lateral thigh microvascular flap. (Used with permission, University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery.)

Reconstruction

Historically, surgeons reconstructed the lateral temporal bone defect by covering the cavity with a split-thickness skin graft.[150] This technique offered patients an option for hearing reconstruction. However, these cavities can develop serious, bothersome drainage and infection especially after radiotherapy. Furthermore, these patients tended to have poor hearing outcomes given the possible chronic infection and sensorineural hearing loss from radiotherapy.

More modern techniques of reconstruction emphasize closing off the cavity from the outside world. The type of reconstruction depends on several factors: size of defect, history of preoperative radiotherapy, vascular and dural coverage, and cosmesis. Small, uncomplicated defects can be reconstructed with temporalis muscle flap.[151] A split-thickness skin graft can be used to cover the flap and to close a small cutaneous defect. However, microvascular free flap reconstruction will be required in most circumstances especially in patients with large skin defects, previous radiotherapy, or when the dura or vascular structures need coverage.[149,152–154]

When facial nerve sacrifice has occurred, nerve grafting should be attempted.[154] Additionally, techniques for facial rehabilitation and eye protection should be considered at the time of the primary surgery. Gold weights, tarsorrhaphy, canthoplasty, brow lifts, and static slings each have a role to play. Oculoplastic surgeons are invaluable members of the team to help prevent or manage eye complications related to facial paralysis.

Osseointegrated implants offer patients an option for hearing restoration and for prosthesis fixation. Implants can be placed either at the time of primary surgery or at a time following completion of therapy. Loading can begin in 3 months in patients not treated with radiotherapy. However, 6 months are allowed to pass before using an implant in an irradiated field.

- Subtotal Temporal Bone Resection (STBR)

Tumors that extend into the middle ear will need surgery beyond the LTBR.[75,82] STBR extends the dissection into the labyrinth, the cochlea, or both. Oftentimes, LTBR is required as an initial first step to permit access to deeper structures.

Skin Incisions

These tumors tend to have their epicenter in the middle ear or mastoid and thus have limited ear canal involvement. A large C-shaped postauricular incision works well. Frozen section is used to confirm a negative ear canal margin, and the ear canal is oversewn.

Bony Dissection

LTBR is performed to remove the disease contained within the ear canal. This gives an unimpeded view of the middle ear, inner ear, and carotid–jugular triangle. Labyrinthectomy, jugular foramen dissection, and cochlectomy are performed as needed depending on disease extent. The eustachian tube mucosa can be involved, and the carotid artery often must be dissected and decompressed. Tumor dissection is performed in a piecemeal fashion. Tissue sampling for frozen section is used liberally to determine the full extent of disease.

The dura of either the posterior or middle fossa is often involved in these tumors. Dural resection is again directed by extent of disease, and frozen section is used to control the margin.

Facial Nerve Management

These patients generally present with facial nerve dysfunction, and these tumors generally involve the facial nerve in its mastoid or tympanic segments. Facial nerve sacrifice is required in this circumstance. Because labyrinthectomy is being performed, the facial nerve can be traced proximally and a tumor-free margin can be obtained. Occasionally, a low-grade tumor, such as an endolymphatic sac tumor or middle ear neuroendocrine tumor, can be adequately dissected away from the nerve and facial function preserved.

Reconstruction Techniques

These procedures generally do not produce large cutaneous defects, but reconstruction is complicated by the presence of a dural defect and the potential for cerebrospinal fluid (CSF) leak. A watertight dural repair should be attempted using allograft duraplasty, but this can be impossible for some defects. Overlay temporalis fascia and abdominal fat graft, as is used in acoustic neuroma surgery, is another option for a small dural defect. Microvascular free flaps can be used, especially in the setting of prior radiotherapy.

- Total Temporal Bone Resection (TTBR)

Although en bloc TTBR has been reported,[155–158] our team does not use this technique. Carotid resection is common to en bloc TTBR, and this carries with it a high morbidity. Our philosophy has been to avoid carotid artery

resection for malignant disease because it produces significant morbidity and does not carry an improvement in overall disease-free survival.

TTBR extends the dissection as described above for STBR and includes removal of the internal auditory canal and petrous apex. Disease removal is piecemeal and directed by frozen section pathology.[75] Reconstruction considerations are similar to those described for STBR.

THE ROLE OF PAROTIDECTOMY AND NECK DISSECTION

External Ear

A persistent controversy in the discussion of SCC of the external ear is the role of parotidectomy and neck dissection. The parotid gland contains lymph nodes that can be the first echelon in metastatic spread from an external ear site. "Currently there is no evidence-based data that supports a mandatory elective parotidectomy in the context of a clinically N0 parotid gland."[11] In the past, authors have surmised that the parotid involvement is low, and therefore, parotidectomy was unwarranted unless clinically involved.[62] Clearly, this discussion revolves around the risk–benefit analysis. The benefits are adequate staging of disease and the potential for durable, recurrence-free survival, whereas the alternative of recurrence following multimodality therapy has a dismal prognosis.

The risks of parotidectomy are well known: facial nerve injury, cosmetic deformity, and Frey syndrome.[159] The incidence of temporary facial paralysis in this setting ranges from 5% to 43%, whereas permanent paralysis is usually <3%.[11,98,160–168]

Osborne et al. studied clinically advanced nonmelanomatous auricular carcinomas. Eleven of these patients had large SCC of the auricle requiring total auriculectomy for excision; 53% of these were recurrent tumors. Clinically and radiographically, these patients all had N0 necks. All underwent elective parotidectomy. Pathologically, none of these patients had metastatic disease. Therefore, the authors concluded that parotidectomy may not be necessary for advanced outer ear cancer when the parotid or external

ear canal is not clinically involved.[11] However, parotid involvement has been found in up to 70% of external ear SCC patients when cervical lymphadenopathy is present.[12]

For the patient with clinically involved parotid gland, cervical lymphadenectomy should be performed because a significant proportion of these clinically N0 necks will harbor occult metastatic disease (30% to 42%).[12,98,169] Selective node dissection, levels II and III, will usually encompass these nodes.[98] In patients with far advanced disease (stages III and IV), a more comprehensive neck dissection is recommended to include even level V lymph nodes.[170]

As a principle, a working facial nerve should be spared unless overtly, macroscopically involved with tumor.[12] Progressive facial palsy, especially isolated branch deficits, in the setting of past skin cancer excision should be viewed with suspicion. This patient will most likely have perineural spread along the facial nerve, producing this deficit. Occasionally, cancer from the sideburn area can travel along the auriculotemporal nerve and can involve both the facial and the trigeminal nerve (see Fig. 23.8).[171]

Rates of facial nerve sacrifice are difficult to compare. Byers et al.[8] noted that 46 out of 486 patients required facial nerve sacrifice. In patients with aggressive cutaneous SCC, facial nerve preservation might be possible in approximately 70% of patients, leaving 30% of patient requiring nerve sacrifice.[98] For the majority of patients, superficial parotidectomy with preservation of the facial nerve will be sufficient to manage suspected metastatic disease within the parotid.[98] Radical parotidectomy with facial nerve sacrifice is indicated for macroscopic nerve involvement or preoperative facial nerve dysfunction.

The role of neck dissection in the clinical N0 neck is a topic of discussion affecting a broad range of tumor types and locations found in the head and neck. Previously, a 20% rate of occult neck metastasis was used as a justification for neck dissection.[172] More recently, the rate to justify neck dissection has been lowered to 15%.[173] Using selective neck dissection rather than radical neck dissection avoids many of complications of radical neck dissection and allows for a lowering of the necessary metastatic rate threshold. Furthermore, neck dissection in the setting of the N0 neck allows for proper staging and for defining the role of adjuvant therapy.[174,175] For

external ear cancers with clinically positive parotid disease, a modified neck dissection including levels II and III is recommended for staging followed by radiation depending on pathologic findings.[175,176]

In the report by Byers et al.,[8] the indication for elective neck dissection required the constellation of initial ear cancer, histologically poorly differentiated tumor, and lesion over 3 cm. His recommendation was for a comprehensive supraomohyoid neck dissection, sparing the spinal accessory nerve, jugular vein, and sternocleidomastoid muscle.

Rowe et al.[86] reported a 45% incidence of nodal metastasis in patients with recurrent skin SCC. In a meta-analysis of 11 articles covering 526 patients with SCC of the ear, an overall rate of metastatic spread to the parotid and upper cervical chain was found in 11.2% of patients.[61]

Regardless, cervical lymphadenectomy is indicated for palpable neck disease and should be considered for patients with recurrent tumors. In this setting, parotidectomy should also be performed. The dictum first promulgated by Byers et al.[8] is that neck dissection should never be performed without parotidectomy in the setting of SCC of the outer ear, and this dictum has been reiterated by others.[9] Other proponents of neck dissection for the N0 neck are found in the literature.[7,9,15,90,97,98,162,169,177]

The role of elective neck dissection for melanoma is perhaps even more controversial. Four large prospective, randomized trials have been performed for cutaneous melanoma and have failed to demonstrate a survival benefit for elective lymphadenectomy.[178–181] In a retrospective review, Byers et al.[54] did not observe a survival difference between elective and salvage neck dissection in melanoma.

Role of Sentinel Lymph Node Biopsy for External Ear Cancers

The role of sentinel lymph node biopsy (SLNB) has yet to be defined for auricular cancers. The rationale for SLNB is to identify potential lymph nodes for sampling in the clinically N0 neck. SLNB has been shown to be effective at determining the rate of occult malignancies in melanoma and some head and neck SCCs.[65,88,92,101,111,182–193]

Cole et al. used SLNB in 9 of 19 patients with auricular melanoma. The

criteria for SLNB in their patient population are not stated, though patients who did have SNLB had thicker lesions (2.30 mm vs. 0.81 mm).[65]

Pockaj et al. reported that 10 of their 78 patients underwent SLNB. All 10 had negative lymph node biopsies, and all 10 remain free of recurrence with a median follow-up of 38 months.[111] They consider SLNB as a highly successful and low-morbidity alternative to elective neck dissection.

Pathak et al.[184] studied lymphatic metastasis from head and neck melanomas. Their study of 169 patients included 20 patients with melanoma of the ear. They found a 100% correlation between the predicted site of involvement and the clinical site of metastatic disease for the primary site, namely, the parotid and cervical lymph node levels 1 through 5. This finding countered a reported 34% discordancy of lymphoscintigraphic positive nodes versus clinically suspected lymph nodes. They further point out that no ear or periauricular melanomas involved postauricular lymph nodes, although lymphoscintigraphic studies showed that postauricular nodes were involved 12% of the time.[194]

Carlson et al. studied SLNB in 58 cases of head and neck melanoma, of which 8 arose from an external ear primary site. Their study demonstrated that lymphatic drainage in these cases was to either parotid or anterior neck nodes and not to posterior neck nodes.[187]

Shpitzer et al.[191] studied SLNB in 15 patients with melanoma of the helix of the ear. Tumor thickness varied from 0.70 to 10 mm (mean 1.2 mm and median 2.13 mm). Sentinel lymph nodes were found in level IIA in 13 of the 15 patients (87%). Four patients (27%) had a sentinel lymph node in the parotid gland. No lymph nodes were found in the retroauricular region. All lymph nodes examined were tumor negative. All patients remained tumor free during a short follow-up (median 39 months, range 12 to 73 months).[191]

Temporal Bone

The parotid gland can be involved either by direct extension through the fissures of Santorini or by metastatic spread to intraparotid lymph nodes.[56,58,195] Morris et al.[56] described a series of 72 patients with temporal bone cancer in whom 36% of patients had direct tumor invasion into the parotid and 25% had metastatic intraparotid lymph nodes. Gidley et al.[26]

found that about 11% of their series of 157 temporal bone cancer patients had salivary gland invasion. For these reasons, superficial parotidectomy, at a minimum, should be performed with LTBR.

Primary tumors of the ear canal, middle ear, and mastoid rarely (around 10%) present with cervical lymphadenopathy.[56,103,196,197] Levels II and III are most commonly involved.[26] Although overall nodal involvement is low, neck dissection and parotidectomy permit accurate tumor staging.[66,198] Neck dissection also facilitates vessel exposure when microvascular free flap reconstruction is needed.

Because the ear canal is more commonly involved by parotid primaries or periauricular skin cancers, parotidectomy and neck dissection are required to address the primary tumor.[199]

COMPLICATIONS OF SURGERY

Temporal bone resection can be associated with high complication rates. All patients are counseled about the risks of surgery: hearing loss, tinnitus, dizziness, facial weakness or paralysis, loss of taste on the tongue, loss of the outer ear, CSF leak, and meningitis. Major complications, defined as requiring additional surgery or additional intensive medical therapy, have remained below 10%. CSF leak and meningitis occur at rates consistent with transtemporal skull base surgery. Pulmonary embolism, myocardial infarction, and death have been reported following temporal bone resection.[26,200] For these reasons, patients must be in good general health to be able to tolerate such surgery.

A maximal conductive hearing loss is the expected outcome of LTBR. This hearing loss can be overcome with an osseointegrated bone-conducting hearing aid. Single-sided deafness (SSD) will occur from STBR and TTBR. Osseointegrated bone-conducting hearing aid or a contralateral routing of sound (CROS) hearing aid is an option for hearing rehabilitation for these SSD patients.

Facial paralysis is a disappointing, but often unavoidable, outcome of temporal bone surgery. Rates of facial nerve sacrifice might be nearly 50% in the setting of advanced disease.[26] Plastic reconstructive surgeons and oculoplastic surgeons are invaluable in helping to manage facial paralysis, to

protect vision, and to restore cosmesis.

CONTRAINDICATIONS TO SURGERY

Surgery is not indicated for patients with unresectable disease, distant metastasis, or poor general health status. Tumors that encase the carotid or vertebral artery, that erode into the cervical spine, or that have significant brain invasion are not considered for surgical treatment. Although the use of carotid artery bypass has been reported for skull base cancers,[201] the long-term results for this technique are disappointing, yielding only a 20% 2-year survival and the attendant risks of postoperative stroke or death[202]. Our team has avoided such surgery and relied on palliative chemotherapy and radiotherapy for these patients.

Isolated and limited temporal lobe involvement can be resected.[157,203] Moffat et al.[204,205] have reported reasonable results following resection of temporal bone tumors with brain invasion. However, in our patient population, we have rarely found isolated brain invasion from temporal bone tumors that did not have concomitant carotid artery involvement or metastatic disease.[26]

TREATMENT—RADIOTHERAPY

Primary Radiotherapy

Radiotherapy has been used either as single-modality therapy or as adjuvant therapy in the postoperative setting. Most surgeons have elected to treat these external ear cancers surgically and to reserve radiotherapy for recurrences or locoregional failures.[8] Elective radiotherapy for external ear cancers lacks high-level supportive evidence.[40] Kwan et al.[206] reported higher rates of locoregional failure in patients with SCC not receiving radiotherapy than in those patients who did.

Primary radiotherapy was used to treat temporal bone cancers up to the 1970s[57,207,208]; however, this technique had a relatively low overall cure rate. Only a few papers have recently reviewed the role of radiotherapy as single-modality therapy.[144,197,209,210] Kang et al.[211] concluded that radiotherapy

alone was not inferior to combined surgery and radiotherapy for disease-specific survival, but they found that local control was worse when radiotherapy alone was used.

Adjuvant Radiotherapy for External Ear Cancers

The majority of patients will be successfully managed with wide local excision achieving negative margins. PORT should be considered for the patient with pathologic indicators: multiple positive lymph nodes (especially if extracapsular spread [ECS] is seen), perineural spread, involvement of named nerve, lymphovascular invasion, or positive or "close margins."[175,176] Byers et al.[8] employed PORT for only five patients and recommend its use when extensive local disease requiring resection of the temporomandibular joint, ascending ramus of the mandible, or temporal bone or total parotidectomy are required.

The role of radiotherapy for external ear cancer and the clinical N0 neck has not been suggested or reported, although there has been proven benefit for other diseases with suspected micrometastasis.[212,213]

However, there is ample evidence of improved locoregional control using PORT for external ear cancers when the indications listed above are present.[214–219] For a dissenting view for PORT, the reader is referred to Gal et al.[39]

Most recent publications suggest 60 Gy in 2 Gy daily fractions as an acceptable dose for PORT[98] and 50 Gy to the undissected neck.[92]

Adjuvant Radiotherapy for Temporal Bone Tumors

Radiotherapy plays a significant role as adjuvant therapy for temporal bone cancers or as treatment for patients who are not candidates for surgery. Advances in skull base techniques vaulted surgery into its current role as primary therapy, using radiotherapy as a postoperative adjuvant.[56,75,220] The combination of these two modalities has improved overall survival for temporal bone cancer patients.[35,153]

Currently, radiotherapy is recommended for T2 and higher-staged tumors.[66,205,209,221] Other indications for PORT include recurrent tumors, positive margins, perineural spread, positive lymph nodes, or extracapsular

spread.[153]

Intensity-modulated radiotherapy (IMRT) allows the radiation oncologist the ability to adequately treat the tumor site while minimizing dose to surrounding structures, especially the temporal lobe and brainstem. Dosages vary widely in the literature. Pfreundner et al.[222] recommended 54 to 60 Gy in patients with negative margins and a minimum of 66 Gy with positive margins. Prabhu et al.[223] gave doses between 60 and 66 Gy for patients with negative margins and doses between 68 and 72 Gy for patients with positive or close margins.

TREATMENT—CHEMOTHERAPY

Advancements in chemotherapeutic agents have ushered in a new era of treatment for head and neck tumors.[224–229] Data from these studies have been extrapolated from mucosal epithelial tumors of the head and neck to other sites. Only a few, isolated studies have examined the role of chemotherapy for temporal bone cancers.[230–232]

Nakagawa et al.[230] described a series of 25 patients with primary SCC of the ear canal and middle ear. Six patients (one patient—T2; three patients—T3; two patients—T4) received preoperative chemotherapy followed by surgery and radiotherapy. Five of these six patients achieved mean survival of 60 months. Chemotherapy and radiotherapy alone were used in seven patients with T4 disease; three of these seven patients had no evidence of disease at mean of 31.6 months.

In a pilot study, Shiga et al.[231] described a series of 14 patients with SCC of the temporal bone of whom 9 had stage IV disease and were treated with concomitant chemoradiotherapy. Their chemotherapy regimen included docetaxel, cisplatin, and 5-fluorouracil (so-called TPF). Eight of nine patients achieved complete response. The authors concluded that the use of concomitant chemotherapy with TPF was safe and effective as treatment for patients with cancer of the temporal bone.[231]

Intra-arterial chemotherapy has been proposed and tested in a very small number of patients. Sugimoto et al.[232] published a small series of five patients with T3 and T4 SCC of the temporal bone who were treated with radiotherapy and intra-arterial chemotherapy consisting of cisplatin and

thiosulfate. Three patients obtained a complete response and had mean survival of 28 months.

SURVIVAL AND RECURRENCE RATES

External Ear

The ear, anterior scalp, forehead, and temple are the most frequent sites of primary SCC in the head and neck.[92] Survival is dependent on locoregional control. Most patients with SCC who experience a relapse will have that relapse in the neck. Therefore, any treatment that improves locoregional control is likely to increase survival.

Neck recurrences develop in a delayed fashion. The median time to develop a nodal metastasis is approximately 12 months,[12] although some late recurrences (between 24 and 36 months) have been reported.[233,234] Recurrence rates for SCC of the ear are higher than are those for other sun-exposed skin sites. Rowe et al.[86] analyzed more than 220 articles and determined a local recurrence rate for ear SCC of 18.7% compared to 7.9% for other body areas. Neck recurrence rates are also higher for external ear (11.0%) than for other body sites (5.2%).[86]

Neck metastasis has a significant impact on overall survival. Byers et al.[8] noted that the 2- and 5-year survival of patients with SCC of the external ear and neck disease was 65% and 46%, respectively. If two or more nodes were found, then survival rates dropped to 57% and 14%, respectively.[8] Interestingly, they found high rates of ECS (93% of patients), although as a single variable for survival, ECS was not as significant as multiple node involvement.[8]

Recurrence following multimodality therapy is often regional (70% to 80%) and often incurable.[235] Recurrence rates in patients treated with multimodality therapy range from 10% to 38% in this setting.[12,92,98,235]

Survival for the patient with recurrent squamous cell cancer following multimodality therapy is poor. Overall survival is 65% at 2 years and 46% at 5 years.[7]

For patients with SCC, Byers et al.[8] could not correlate local or regional

failure or survival to patient age, gender, type of neck dissection, site of primary cancer, site of nodal metastases, or histologic findings. In his study, 6% of patients presented with N1 neck and another 6% of patients developed neck metastases within 24 months of treatment.[8]

Lymph node metastasis is associated with lower 3-year disease-free survival, disease-specific survival, and overall survival.[98] Published studies of external ear SCC is presented in **Table 23.6**.

Table 23.6 Compilation of Published Reports of SCC of the External Ear

Authors	Year	Total No. Patients	Median Age, Years (Range)	Parotid Metastasis Rate at Presentation	Neck Metastasis Rate at Presentation	Local Recurrence Rate	Regional Recurrence Rate	Distant Metastasis Rate	Overall Survival	Mean F/U, Months
Byers et al.[8]	1983	486	68 (16–98 y)	NS	6%	14%	6%	1%	68% at 2 y 48% at 5 y	
Freedlander and Chung[47]	1983	160	72 y (range NS)	9.4%	11.3%	17%	13%	NS	93% (F/U more than 12 mo)	NS
Shockley and Stucker[16]	1987	75	66 (range NS)	NS	NS	12.5%	10%	2.5%	93% (F/U NS)	NS
Mohs et al.[121]	1988	871	NS	NS	NS	NS	NS	NS	92.3% (5-yr cure rate)	
Yoon et al.[7]	1992	40	71 (43–93 y)	NS	10%	22.5%	20%	7.5%	70% at 5 y	NS
Thomas and Matthews[17]	1994	44	76 (61–91 y)	NS	0%	14.8%	9.3%	NS	NS	NS
Silapunt et al.[18,a]	2005	117	71 (34–90 y)	NS	NS	3.4%	2.6%	NS	NS	NS
Turner et al.[12]	2009	43	72	56%	30%	32.5%	2.3%	0%	51%	35 mo
Peiffer et al.[170,b]	2011	41	74.2 (20–97)	24.4%	43.9%	46.3% (overall)	NS	NS	60% at 5 y	18 mo

Parotid and neck metastasis rates are at presentation.

[a]Mohs micrographic surgery technique.

[b]Stage III and IV patients only.

NS, not stated.

Temporal Bone Cancer

Historically, temporal bone tumors were associated with dismal results and a poor prognosis.[236,237] However, advancements in multiplanar imaging, skull base surgical techniques, IMRT, and chemotherapy have combined to improve overall survival. A cogent staging system, as proposed initially by Arriaga et al.[81] and later modified by Moody et al.,[19] has allowed comparison of results across time and institutions. This later iteration of the Pittsburgh staging has demonstrated that survival is progressively worse with increasing T stage,[74] and this finding is supported by other papers.[66,197,238] The

Pittsburgh tumor staging is an important, independent factor for prognosis and a reliable predictor for outcomes for SCC.[66]

Small tumors that are limited to the ear canal with minimal soft tissue involvement or bone erosion (i.e., T1 and T2 tumors) can be completely excised with LTBR. Whereas T1 tumors can be treated with surgery alone, T2 tumors have improved outcomes when PORT is added.[66,209] These patients with early-stage disease enjoy 80% to 100% 5-year survival rates.[33,75,239,240]

Larger tumors (T3 and T4) involve significantly more anatomic structures and present a significantly more difficult tumor to treat. These tumors can be conceptualized in two varieties: external ear canal tumors that erode past the eardrum into the middle ear and tumors that arise primarily within the middle ear, inner ear, or mastoid. When tumors involve the middle ear, the LTBR is no longer an adequate or sufficient surgical treatment.[241] Multidisciplinary team management is required for these larger, advanced-staged tumors. These patients might require a combination of surgery, radiotherapy, and chemotherapy for treatment of their tumors. Treatment goals remain consistent despite the large size of the tumor: adequate disease resection to achieve negative margin while minimizing damage to surrounding normal structures. Despite adequate treatment, overall 5-year survival rates do not exceed 50% for this group of late-stage tumors (**Table 23.7**).

Table 23.7 Comparison of Recently Published Survival Results for Squamous Cell Carcinoma (SCC) of the Ear Canal and Temporal Bone

Authors (Year)	Total Patients (n)	T Stage* (n)	Mean FU (Months)	Overall 5-Year Survival (%)	Disease-specific Survival (%)	Disease-Free Survival (%)
Yin et al. (2006)[197]	95	NS	NS	66.8% (cohort) Stage I = 100% Stage II = 100% Stage III = 67.2% Stage IV = 29.5%	NS	NS
Madsen et al. (2008)[238]	47	T1 = 13 T2 = 7 T3 = 7 T4 = 19	48	31%	42%	NS
Kang et al. (2009)[211]	35	T1 = 10† T2 = 11 T3 = 14	34	NS	80% (3 y)	63% (3 y)
Prabhu et al. (2009)[223]	30	T1 = 7† T2 = 5 T3 = 18	24	54%	T1&T2 = 70% T3 = 41%	T1&T2 = 73% T3 = 55%
Gidley et al. (2010)[66]	71	T1 = 20 T2 = 15 T3 = 5 T4 = 31	NS	38%	NS	60%
Chi et al. (2011)[33]	72	T1 = 15 T2 = 3 T3 = 19 T4 = 35	NS	T1 = 100 T2 = 66.7 T3 = 21.1 T4 = 14.3	NS	NS
Bacciu et al. (2013)[75]	45	Stage I = 5 Stage II = 6 Stage III = 15 Stage IV = 19	46.7		Stage I = 100% Stage II = 100% Stage III = 65.1% Stage IV = 59.6%	

Only studies with 30 or more patients are included.

*Pittsburgh 2000 staging system[19] is used except where noted by † for Stell and McCormack staging system.[80]

Facial nerve involvement, positive lymph nodes, extratemporal disease extension, and positive surgical margins are all factors linked with poor overall survival.[26,30,33,56,197,238] A systematic review of SCC of the temporal bone showed that 5-year overall survival dropped to 19.1% in patients with facial paralysis versus 59.4% in patients without facial paralysis, regardless of tumor stage.[74]

Although lymph node metastases are uncommon, their presence is a significant risk factor for poor survival.[26] For patients with SCC, Morris et al.[56] reported that 5-year disease-specific survival (DSS) was 81% in node-negative patients and 19% in node-positive patients ($p < 0.0001$).

Margin status is a strong predictor for recurrence, and rates of positive margins vary between 20% and 33%.[26,33,56,66,197,238] Morris et al.[56] describe 5-year DSS of 81.7% for patients with negative margins versus 50.0% for patients with positive margins ($p = 0.03$, log rank).

Other factors that are linked to high recurrence rates and poor survival include such factors as middle ear invasion,[238] need for mandibulectomy,[26,56] performance of craniotomy, dural involvement,[75] facial nerve sacrifice, and parapharyngeal space or infratemporal fossa dissection.[242] Middle ear invasion is an important factor, because tumors that are confined to the ear canal can be resected en bloc with LTBR. Survival rates decrease to about 20% when the middle ear is involved with tumor compared to 60% or higher when the middle ear is not involved.[57,75,238]

Intracranial disease extension can be successfully treated.[200,205] Dural involvement was seen in about 5% of patients from a series of 157 temporal bone cancer patients.[26] Dean et al.[153] found intracranial disease in 16 out of 65 patients, and they found that it did not have an effect on disease-free survival. The local control rates were similar with or without intracranial extension (76.9% vs. 71.7%, respectively).[153]

Recurrences tend to occur within the first 2 years following completion of therapy and are a major cause of mortality.[26,56,75] A large study of 157 patients with temporal bone tumors showed a mean time to recurrence of 13 months.[26] In this study, recurrences were 12.7% local, 6.4% regional, and 13.4% distant. The most common sites for distant spread are lung, brain, and dermal metastases.[26] Morris et al.[56] showed recurrence rates of 20.5% for local disease, 5.5% for regional disease, and 22.9% for distant disease. Recurrence rates tended to be higher with salivary gland origin tumors.

Because temporal bone tumors are rare, many authors have lumped several different tumor histologies into analysis.[26,56] This lumping can make analysis difficult because tumor biology and behavior vary widely among these histologies. A clear distinction in tumor behavior exists between SCC and ACC. Although SCC is the most common tumor type, it has a lower overall 5-year survival rate than is reported for ACCa of the ear canal.[66,69,243,244] Whereas mean time to recurrence with SCC is around 2 years, the mean time to recurrence for ACCa is reported to be nearly 8 years.[66,69]

CONCLUSIONS

The external ear is a frequent site of skin cancer, and it carries a relatively

high risk compared to other sites for cutaneous malignancy. SCC and BCC occur at nearly equal frequency. Early-stage cancers can generally be cured with surgery that achieves negative margins. A variety of surgical approaches and reconstructive options are available for these early-stage tumors. Advanced-stage tumors require more aggressive status perhaps including total auriculectomy, LTBR, parotidectomy, and neck dissection. The roles of elective parotidectomy and neck dissection are controversial when these areas are not clinically involved. Radiotherapy is useful as a postoperative adjuvant for advanced tumors and as an alternative to surgery in sickly patients.

Ear canal and primary temporal bone tumors are rare. The temporal bone is more likely to be involved secondarily by tumors from the parotid gland or periauricular skin. Suspicious lesions of the ear canal should be biopsied for proper diagnosis. The most common tumor type is squamous cell cancer; however, a long list of tumor types has been described involving the temporal bone.

Surgical resection to achieve negative margins is the mainstay of treatment. Small tumors (T1 and T2) can oftentimes be treated with LTBR. Parotidectomy and neck dissection are added for disease extension and proper staging. Higher-staged tumors, T3 and T4, will generally require STBR or TTBR along with possible craniotomy, mandibulectomy, resection of the zygoma, and dissection of the infratemporal fossa.

Small defects can be adequately reconstructed with a temporalis muscle flap. Microvascular free flaps are used for large defects and for patients with a history of prior radiotherapy. Adjuvant PORT has demonstrated improved survival for patients with temporal bone tumors staged T2 or higher. Chemotherapy has an emerging role for advanced-stage disease. Evaluation and management of patients with temporal bone tumors by a multidisciplinary team are critical in order to optimize outcomes in this group of patients

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24 Cancer of the Head and Neck in the Pediatric Population

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Introduction

Epidemiology

It is estimated that 15,780 new cases of cancer and 1,960 cancer-related deaths occurred among children and adolescents below age 20 in the United States in 2014.[1] Tumors of the head and neck region account for 5% to 10% of all childhood malignancies.[2,3] Similar to other childhood cancers, the incidence of head and neck malignancies in the pediatric age group has demonstrated apparent increases in the United States in recent decades.[2] Given the potential for pediatric head and neck tumors or their treatment to adversely affect critical structures, functional outcomes, and quality of life, coupled with the rarity and diversity of many such tumors, multidisciplinary team management with expertise specializing in pediatric cancer is obligatory.

In an analysis using the National Cancer Institute's population-based tumor registry, Surveillance, Epidemiology, and End Results (SEER), 3,050 children younger than age 19 years with head and neck tumors were identified from 1973 through 1996. Dominant histologic categorizations included lymphoma (27%), neural tumors (including neuroblastoma and retinoblastoma, 23%), thyroid cancers (21%), and soft tissue sarcomas (12%). The most common individual diagnoses were papillary thyroid carcinoma (*n* = 537), Hodgkin lymphoma (HL) (*n* = 515), retinoblastoma (*n* = 497), non-

Hodgkin lymphoma (NHL) (*n* = 301), and rhabdomyosarcoma (*n* = 239). Unlike cancers of the head and neck among adults, squamous cell carcinomas in pediatric patients are rare, accounting for fewer than 2% of cases.[2] Another recent analysis, looking only at sarcomas of the head and neck in the SEER database from 1973 through to 2010, identified 1,244 pediatric cases (including up to age 19 years) and 11,481 adult cases, with 10-year survival of 71% in pediatric patients compared to 61% in adult patients.[4] In this analysis of head and neck sarcomas, the most commonly reported histologies were rhabdomyosarcoma (48%), malignant fibrous histiocytoma (MFH, 11%), osteosarcoma (8%), and Ewing sarcoma (6%).[4]

The age of presentation can provide important initial guidance for conditions likely to be malignant arising in the head and neck. From the SEER database, retinoblastoma, neuroblastoma, germ cell tumors, and rhabdomyosarcoma are among the most common conditions among neonates and infants.[2] Among children below age 10 years, one can see various conditions, including NHL and HL. Among children and adolescents above age 10 years, dominant malignancies of the head and neck include thyroid cancer, Hodgkin and non-Hodgkin lymphoma, and melanoma.[2] Certain tumors are rarely seen outside of their typical age of presentation, including malignant germ cell tumors involving the head and neck, which are mainly seen only in neonates or infants,[5] and retinoblastomas, which are rarely seen in children older than 5 years.

Of note, clinical reviews of malignancies of the head and neck do not consistently include important differential diagnoses such as retinoblastoma in the pediatric age group, and leukemia presenting with chloromas. In addition to primary cancers arising in the head and neck, conditions such as malignant germ cell tumor, lymphoma, and neuroblastoma may also metastasize to the nodes, soft tissue, or bones of the head and neck.

Secondary malignant tumors of the head and neck, that is, those resulting from prior therapy including radiation therapy and alkylating chemotherapy agents, account for about 0.8% of tumors of the head and neck in the pediatric age group[2] and may include thyroid carcinoma, osteosarcoma, MFH, and salivary gland tumors.[6,7]

Diagnostic Evaluation: An Overview

As most masses in the head and neck in pediatric age group are benign, careful clinical history and physical examination with additional workup when appropriate are warranted to diagnose patients with malignant lesions. Conditions to be considered include lesions primarily arising in the head and neck, those that are metastatic to the head and neck, and secondary malignancies. Primary head and neck lesions can include congenital or developmental lesions, inflammatory or infectious masses, benign tumors, or malignant tumors (**Table 24.1**).

Table 24.1 Sample Differential Diagnoses for Head and Neck Masses

Common Presenting Site	Differential Diagnoses[a]			
	Congenita	**Inflammatory/Infectious**	**Benign Tumors**	**Malignant Tumors**
Lateral neck mass	■ Cervical rib ■ Branchial cleft cyst	■ Reactive lymphadenopathy (e.g., viral, bacterial, mycobacterial, granulomatous) ■ Sialadenitis	■ Focal myositis ■ Torticollis ■ See nonlocalized	■ Hodgkin lymphoma ■ Non-Hodgkin lymphoma ■ Retinoblastoma
Midline neck mass	■ Thyroglossal duct cyst ■ Dermoid cyst ■ Thymic cyst ■ Lymphatic Malformation	■ Thyroid disease	■ Thyroid nodule ■ Tracheal and endobronchial tumors ■ Parathyroid adenoma ■ Paraganglioma	■ Thyroid carcinoma ■ Tracheal and endobronchial malignancies ■ Parathyroid carcinoma ■ Malignant paraganglioma
Nonlocalized or various	■ Vascular malformation	■ Ludwig angina ■ Abscesses	■ Hemangioma ■ Lipoma ■ Fibroma ■ Neurofibroma ■ Lymphangioma ■ Salivary gland tumors	■ Hodgkin lymphoma ■ Non-Hodgkin lymphoma ■ Thyroid carcinoma ■ Rhabdomyosarcoma ■ Neuroblastoma ■ Nasopharyngeal carcinoma ■ Germ cell tumor ■ Desmoid tumor ■ Salivary gland malignancies ■ Skin malignancies ■ NUT midline carcinoma ■ Metastatic cancer

[a]Note that variants of some conditions may appear in more than one category.

Assessment of a child with a mass in the head and neck should start with a detailed clinical, past medical, and family history, immunization history, and recent and current medications. History should detail the onset, nature, and timing of any changes associated with the mass, along with potential exposures and risk factors for infection (e.g., tuberculosis), travel, and exposure to animals (e.g., zoonoses).

Congenital or developmental lesions may first be evident in the early postnatal period, but in some cases they can manifest later in life, with gradual growth over time or with concomitant secondary infection. Benign

tumors can similarly sometimes be brought to medical attention in the setting of concurrent infection. Whereas inflammatory/infectious etiologies are typically first considered for masses that acutely enlarge and are associated with acute fever, tenderness, or skin changes such as erythema or warmth, red flags should prompt consideration of an underlying malignancy. Potential red flags include firm, fixed/immobile or large (>1.5 to 2 cm) masses; lymph nodes in atypical locations (e.g., supraclavicular) or multiple locations; masses initially queried to be inflammatory or infectious in nature that do not respond to initial empiric management or persist beyond 4 to 6 weeks; or constitutional symptoms such as malaise, weight loss, anorexia, and unexplained fevers or night sweats.

Relevant clinical and functional impairments to assess on history and to observe on examination may include abnormal eye movements; distorted vision; proptosis; Horner syndrome; cranial nerve palsies; paresthesias; recurrent epistaxis; increasing nasal congestion; evidence of recent suspected/confirmed infections; loss of smell; stridor; dysphagia and odynophagia; impaired gag; trismus; deviated tongue; dental health; change in tooth position; change in voice or hoarseness; otorrhea; progressive tinnitus or hearing loss; otalgia; vertigo; neck tilt or torticollis; facial and/or neck swelling; deviated trachea; increased vascular markings, pulsatility, or overlying skin changes; or features of hypothyroidism or hyperthyroidism.

Physical examination should also include evaluation for movement of the mass with tongue protrusion (e.g., thyroglossal duct cysts, which typically move upward with tongue protrusion) and include a full systemic examination for systemic lymphadenopathy, with particular vigilance for lymph nodes in atypical sites such as the supraclavicular area or that are firm, fixed, and significantly enlarged; ophthalmologic examination; assessment of tonsillar tissue; oral mucosal examination; thyroid examination; cardiorespiratory examination; abdominal examination for masses or hepatosplenomegaly; genitourinary examination; skin examination for evidence of petechiae or purpura or neurocutaneous markings; dysmorphic features; detailed neurologic examination; and note of any current or impending functional impairment from mass effect.

Any concern for potential airway compromise must be immediately evaluated and managed as an oncologic emergency. As tumors in the head and neck may expand into cavities such as the maxillary sinus with relatively

limited innervation, pain is not necessarily a dominant symptom and more likely becomes prominent with nerve compression or periosteal impingement.[8] Potential intracranial extension, with intraparenchymal brain metastasis or leptomeningeal disease, can also be seen in children and may also be associated with varied acute neurologic symptoms, warranting careful evaluation and management.[8,9] Careful clinical and radiologic assessment as appropriate for a potential mediastinal mass should also be pursued, and managed as a medical emergency, given the risk of acute cardiorespiratory decompensation with sedation or suboptimal body positioning. Once oncologic emergencies have been ruled out or definitively managed, a broad differential diagnosis should be considered.

Targeted laboratory studies should be considered to further evaluate suspected conditions based on initial history and physical examination. Evaluations for persistent adenopathy not responsive to empiric antibiotics may include considerations for *bartonella henselae* (catscratch), Epstein-Barr virus (EBV), cytomegalovirus, toxoplasmosis, histoplasmosis, tuberculosis, and human immunodeficiency virus as appropriate.

Targeted imaging should also be considered to help with diagnosis and further management planning, with sample modalities outlined in **Table 24.2**. For children (up to age 14) with a mass in the neck or adenopathy, the American College of Radiology (ACR) Appropriateness Criteria recommends the use of neck ultrasound as the most appropriate modality, followed by computed tomography (CT) of the neck (with contrast) and magnetic resonance imaging (MRI) of the neck (without and with contrast).[10] Although intravenous contrast is typically recommended with cross-sectional imaging to help characterize the margins of the lesions and abnormally enhancing lesions that may not be pathologically enlarged, this should be considered in conjunction with a specialist team that includes a radiologist. For instance, noncontrast CT is recommended in the setting of suspected salivary gland enlargement due to a sialolith,[10] whereas for a suspected mass in the thyroid, use of iodinated contrast agents is typically avoided or used judiciously only after discussion as a specialist team, as iodine uptake in the thyroid may affect timing of subsequent diagnostic or therapeutic steps.

Table 24.2 Sample Role of Imaging Modalities for Head and Neck Masses

Imaging Modality	Considerations for Use	Typical Uses
Neck ultrasound (US)	■ Helpful to assess solid vs. cystic palpable lesions ■ Can help define location, shape, size ■ No ionizing radiation	■ Initial evaluation of most pediatric neck masses, including suspected thyroid nodule[10] ■ May be performed as a guidance study to facilitate biopsy
Neck ultrasound with Doppler	■ Helpful with characterizing vascularity, and blood flow in solid lesions ■ No ionizing radiation	■ Queried vascular lesion or malformation ■ Initial evaluation for queried vascular occlusion
Computed tomography (CT), neck	■ Typically requested in discussion with specialist team ■ For suspected thyroid mass, consult specialist team prior to using iodinated contrast media ■ Noncontrast CT recommended for suspected sialolith[10] ■ May require sedation	■ Preferred evaluation for retropharyngeal mass[10] ■ May be performed as a guidance study to facilitate biopsy of potential malignant or nondefinitive lesion in deep or challenging locations
Magnetic resonance imaging (MRI), neck	■ Typically requested in discussion with specialist team ■ No ionizing radiation ■ May require sedation with typically longer examination time than other modalities	■ Can be helpful for further evaluation of certain lesions, including vascular malformation, after initial ultrasound, or for further soft tissue and perineural delineation

A chest radiograph, which is readily available, can be useful for particular circumstances. These can include situations when one suspects a mediastinal mass, an oncologic emergency that requires care in patient positioning during the evaluation, as well as for suspected lesions extending into the chest or for gross metastatic disease.

Specialized imaging such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), CT or magnetic resonance angiography, or other body imaging is typically reserved for confirmed malignancies in the setting of staging or follow-up evaluation. Key considerations for imaging in children with head and neck malignancies are outlined in **Table 24.3**, with more detailed depictions in the sections and references below.[11–17] In all cases, the concept to "image gently" and expose children to "as low as reasonably achievable" (ALARA) levels of ionizing radiation in imaging should guide practices.[16,18]

Table 24.3 Common Imaging Modalities for Selected Primary Malignancies in the Head and Neck

Head and Neck Diagnosis	US	CT	MRI	PET-CT	mIBG	Bone Scan	Other Considerations
Rhabdomyosarcoma		•	•	•		•	
Desmoid tumor			•				
Bone sarcomas		•	•	+/–		•	
Hodgkin lymphoma		•		•			
Non-Hodgkin lymphoma		•	•	+/–		•	
Nasopharyngeal carcinoma		•	•	+/–		•	Dental x-ray
Neuroblastoma		•	•		•		
Esthesioneuroblastoma	•	•	•	+/–		•	
Retinoblastoma	•		•				
Salivary gland tumors	•		•				
Thyroid carcinoma	•		•				Radioactive iodine scan[a]
Malignant germ cell tumor		•	•			•	
Paraganglioma			•	•	•		Octreoscan

Note: These are potential options for staging and/or monitoring of primary malignancies in the head and neck that have been described in the literature, by consensus groups or in conventional protocols for children; other modalities may be needed as clinically indicated, including modalities and specification of anatomic sites for full metastatic evaluation. Not all options may need to be used for a single patient. Primary presentations of the same diagnosis outside of the head and neck may also preferentially warrant other modalities.

[a]For select differentiated thyroid carcinoma patients only.

Early consultation with a multidisciplinary specialist team, including providers in pediatric surgery and pediatric hematology/oncology, is warranted for any concerns of potential malignancy.

Fine-needle aspiration (FNA) may be considered for initial tissue evaluation of selected neck lesions of children, with sensitivity ~90% or higher, and specificity ~85%, where the most likely diagnosis is reactive lymphadenopathy.[19,20] Advantages include its minimally invasive nature compared to an open biopsy, relatively low cost, and potential avoidance of general anesthesia in some children.[3,19,20] Anticipatory multidisciplinary planning prior to any potential biopsy is recommended, including at least the surgical, radiology, and pathology teams, as image guidance and rapid on-site processing could critically impact diagnostic yield. With the aid of experienced pediatric cytopathology team members, FNA or core needle/open biopsy specimens can be processed for rapid interpretation with direct smears and cell block preparation for routine hematoxylin and eosin-stained slides, as well as ancillary studies, which can include cultures, special stains for acid-fast bacilli or fungi, flow cytometry, or fluorescent in situ

hybridization.[20] Core needle or open biopsies are recommended when malignant disease is likely, bony lesions are suspected, or preserved tissue architecture or more complete evaluation of suspected heterogeneous tissue (which may be missed by selective FNA sampling) are required for diagnostic confirmation or where FNA sampling was insufficient, indeterminate, or inconsistent with the clinical impression.[8,20]

Clinical Management: An Overview

Optimal management of malignant tumors in the head and neck conditions requires a coordinated multidisciplinary team with familiarity and dedicated expertise in working with children with these rare and complex cancers. Inherent in the very location of tumors of the head and neck and their proximity to multiple vital structures, this group of tumors warrants anticipatory evaluation and management of potential airway compromise and special anesthesia needs and potential functional implications of the mass in its natural course, as well as implications secondary to diagnostic and therapeutic procedures, while considering the child's developmental growth and function.

Functional sequelae to be considered and optimally prevented may include more immediate concerns involving compromised swallowing and the risk of aspiration or ophthalmologic complications,[21] as well as longer-term implications of the cancer or therapy on orofacial development and dentition,[22,23] jaw function,[24] cosmesis, and cognitive function. For instance, patients with a history of dysphagia would benefit from clinical bedside swallowing evaluation by speech language pathologist, as well as barium swallow examination if clinically indicated.

Vigilant supportive care is also required to evaluate and address the known toxicities of cancer therapy that may be exacerbated by the location of the tumor of the head and neck, including oral mucositis. Young patients require nutritional and growth monitoring and may benefit from feeding tubes for enteral nutrition as well as for selected administration of medication. As many effects of the cancer therapy may initially become manifest or progress months or years beyond the treatment period, long-term follow-up for potential late effects is warranted.

Updated general guidance for the core personnel and resources essential

to provide care for children and adolescents with cancer has been recently articulated by the American Academy of Pediatrics. Outcomes for children with malignancy have been demonstrated to be better when core management is at least initiated by specialist pediatric cancer centers.

Typical specialist multidisciplinary team members engaged closely with families of children with malignant masses in the head and neck should include pediatric physicians, nurses, pharmacists, social workers, and other allied health team members working in hematology/oncology; surgery, otolaryngology, and neurosurgery; ophthalmology; dental oncology and orthodontics; radiation oncology; plastic and reconstructive surgery; radiology and diagnostic imaging; pathology; nutrition; speech/language pathology; and child life. In many cases, the expert consultative input of other pediatric team members in anesthesiology, critical care, endocrinology, genetics, infectious diseases, neurology, ocular prosthesis, palliative care, psychology, rehabilitation specialists including occupational and physical therapy, and team members experienced in late effects of therapy is also invaluable. In all cases, the pediatric patient, the family, and the community-based or primary care team members engaged by the family remain central partners with the multidisciplinary specialist team in decision-making and family-centered care delivery.

Surgical Considerations: An Overview

Surgical management of pediatric age group cancer of the head and neck has undergone many significant changes during the past two decades. Most of these changes have occurred as a result of technologic advances, including better imaging, more precise delivery of radiation, advances in surgical technique, and a better understanding of anatomy. The improved understanding of anatomy has had its greatest impact on the development of better and more reliable reconstructive techniques that allow us to perform surgery that, in the past, would have been impossible. We can now be more certain that the defects that we create surgically can, for the most part, be reliably reconstructed. However, in the pediatric age group, cancer of the head and neck is uniquely affected by the need to account for the growing and developing facial skeleton and associated structures. This has a particular impact in children’s dentition, which owing to its continued growth until skeletal maturity often requires a staged approach to reconstruction.

Evaluation for surgery is first dependent on accurate tissue diagnosis, requiring incisional or excisional biopsies for the vast majority of solid tumors. Exceptions include salivary or thyroid masses, for which fine needle aspiration is an option. Subsequent staging evaluation includes routine laboratory studies (complete blood count, basic metabolic panel, liver function tests, lactate dehydrogenase [LDH]), CT scan of the chest, and in many cases positron emission tomography (PET) scan. Unlike in cancer in adults, pediatric resections must balance the extent of surgical resection with functional and aesthetic concerns, and thus, radical resection with negative margins (R0) resections is not always possible. Some pediatric tumors, in fact, are so responsive to nonsurgical therapies or are so indolent in nature (e.g., desmoid tumors) as to make resections unnecessary. As with adult malignancies, patients are frequently candidates for either chemotherapy and/or radiation therapy in either a neoadjuvant or an adjuvant setting. Depending on the pathology of the disease, timing of such treatment may vary. Finally, reconstructive concerns share many similarities with cancers in adults, but have specific differences with regard to the developing pediatric facial skeleton and associated structures.

Role of Radiation Therapy: An Overview

Radiotherapy is a critical component of the multimodality management in the pediatric age group of cancer of the head and neck. Although some tumors involving the head and neck are surgically accessible, complete extirpation of lesions occupying anterior craniofacial spaces or the base of the skull is often impossible without significant morbidity necessitating a management plan that relies on nonsurgical modalities either as surgical adjuncts or for definitive tumor control. Microscopic residual disease is a source of local failure that can be addressed via the use of adjuvant radiotherapy or chemoradiotherapy. Clinical studies of pediatric head and neck cancer seek optimal combinations of multimodality therapy in order to reduce late effects while simultaneously increasing rates of long-term disease control.

Conformal radiotherapy with or without intensity-modulated radiation therapy has been the primary mechanism of radiation dose delivery during the past two decades.[25,26] Advances in software now routinely employ computation-heavy, cost–benefit function analyses of beam modulation to address irregular structures within the body, particularly when they are

concentrically contained within or encapsulated by normal organs with dose-limiting sensitivity to radiation effect.[27,28] Furthermore, physiologic motion is minimal within the head and neck region, allowing greater confidence in patient setup and targeting the tumor bed. Although some advances, like respiratory gating and breathing management (deep inspiration breath hold), have been developed to address organ and target volume motion, most treatment of the head and neck in the pediatric age group can be accomplished without resorting to these specialized measures.[29] Prosthetics in the form of intraoral molds and the use of thermoplastic head and neck immobilization devices frequently serve as positioning aids, both internally and externally for the pediatric oropharynx and head/neck, respectively.[30,31] Fiducial markers can also be implanted to further aid in targeting when extraordinarily high precision is required to spare critical structures skirting radiation dose thresholds.

Frequently, these tumors afflict young children and infants requiring sedation to achieve adequate immobilization suitable for treatment. Most institutions choose to sedate with propofol and avoid airway management when possible, although occasional management of the airway is required to ensure patient safety through a full course of radiation, as determined by the anesthesiologist.[32]

Proton therapy has recently become central to the discussion of pediatric radiotherapy due to the promise of reduced toxicity; larger-scale clinical trials designed to demonstrate the potential advantages are ongoing. Although a major objective of proton therapy is reduction of toxicity, protons do not inherently promise a more efficacious means of disease control (unless normal tissue sparing through improved tumor targeting is enhanced such that dose escalation of residual tumor can result in improved disease control).[33] At this time, precision targeting with proton beam is still developing as a routine component of clinical practice due to various factors, including cost and accessibility. Proton therapy requires prospective study design to provide evidence for the appropriate indications and degree of benefit that may be obtainable.

DISEASE-SPECIFIC OVERVIEW:

DIAGNOSIS, STAGING, TREATMENT, AND PROGNOSIS

Rhabdomyosarcoma

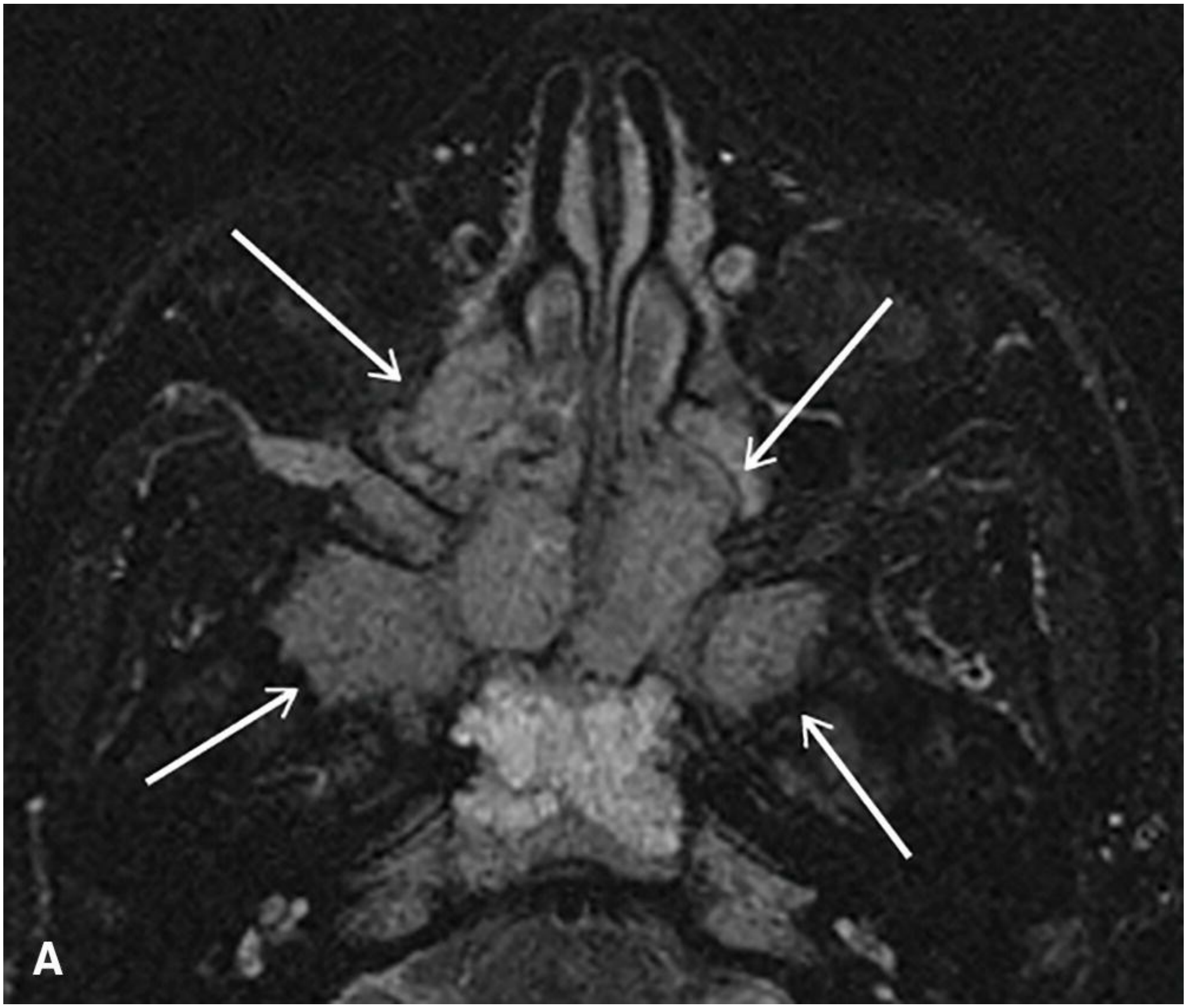
Rhabdomyosarcoma is the most common pediatric soft tissue sarcoma, with an overall annual incidence in the United States of 4.5 cases per million children and adolescents, with the majority occurring in children younger than 10 years.[34] It arises as a primary malignancy in the head and neck in ~35% to 40% of cases, most commonly in the orbit.[3,4,8,21] Cooperative group efforts, including the Intergroup Rhabdomyosarcoma Studies (IRS), have contributed to the advances in management. The mainstay of therapy is multimodal, including multiagent systemic chemotherapy for all patients and either radiation therapy, surgery, or both, as local control for most patients. Across the pediatric age spectrum, outcomes for patients who have rhabdomyosarcoma have improved since 1975, with 5-year survival rates increasing by more than 10% to ~65% or higher for patients younger than 15 years old and to ~50% for patients 15 to 19 years old.[35]

Rhabdomyosarcoma encompasses two main histologic subtypes: embryonal and alveolar. The embryonal subtype is the most common among children, noted in approximately two-thirds of the patients, with common locations including the head and neck and the genitourinary tract. Botryoid and spindle cell variants of embryonal rhabdomyosarcoma have a particularly favorable prognosis.

Within the head and neck, rhabdomyosarcomas are further classified as originating from the orbit (including eyelid), parameningeal (including middle ear/mastoid, nasopharyngeal/nasal cavity, paranasal sinus, parapharyngeal region, and pterygopalatine/infratemporal fossa), or nonparameningeal sites (including the scalp, ear lobe, parotid, oropharynx, and hypopharyngeal region).[8,36] Key prognostic factors for pediatric patients with rhabdomyosarcoma are used by the Children’s Oncology Group (COG) to categorize patients into three risk groups (low, intermediate, and high) based on risk of disease recurrence. Standard prognostic factors include age (best age 1 to 9 years), primary site (favorable sites including orbit, nonparameningeal head and neck, genitourinary sites excluding bladder and

prostate, and biliary tract), tumor size (smaller, ≤5 cm better), tumor resectability, disease spread (better prognosis with localized disease without regional lymph node involvement or distant metastases), and tumor histopathology (embryonal more favorable than alveolar subtype).[36] In recent years, ~80% of alveolar rhabdomyosarcomas have been found to harbor a fusion of the FOXO1 gene (on chromosome 13) with either the PAX3 or PAX7 genes (on chromosome 2). As the presence of FOXO1 gene fusion status is more closely associated with adverse outcomes, in upcoming COG trials, FOXO1 fusion status is anticipated to replace histopathology classification in risk stratification criteria.[37]

Presentation of rhabdomyosarcomas can vary greatly depending on the primary site and typically require an open or core needle biopsy to confirm histopathologic and molecular diagnosis. Radiologic staging has typically included a baseline chest radiograph, chest CT, bilateral bone marrow aspirates and biopsies, and bone scan (with some centers opting for PET–CT in lieu of bone scan). For patients with parameningeal primary tumors, in particular, an MRI of the brain and skull base is required, and baseline lumbar puncture for malignant cells in the cerebrospinal fluid should also be obtained. MRI with MRA/MRV may be used to evaluate the relationship of the tumor to nearby vascular structures. Suspected spinal cord involvement can be investigated with MRI including contrast. Rhabdomyosarcomas of the head and neck have a variable imaging appearance but are often heterogeneous and may contain areas of necrosis and/or hemorrhage. They often erode adjacent bone and may extend intracranially. There are no pathognomonic imaging findings (**Figs. 24.1** and **24.2**).[38]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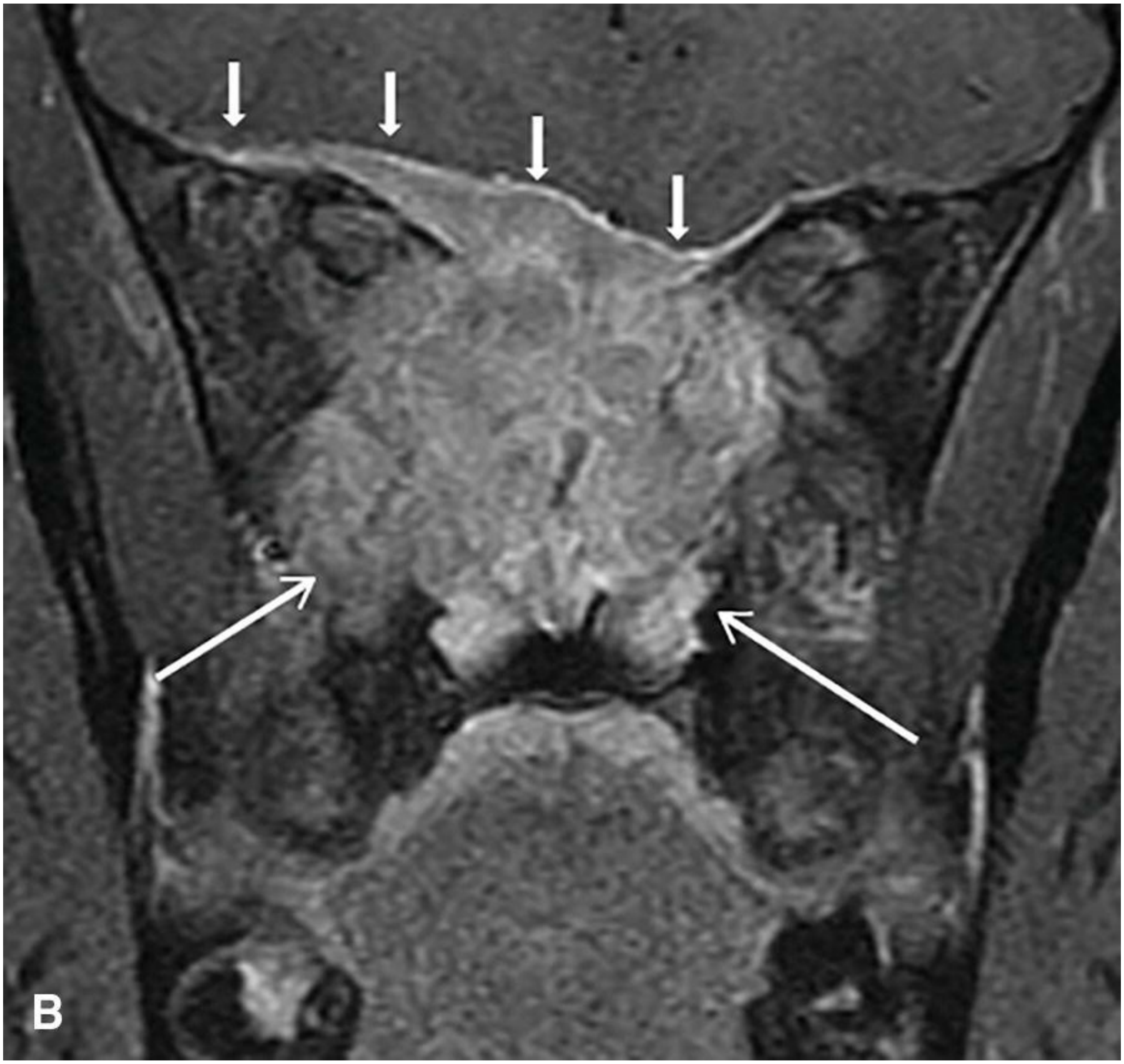

Figure 24.1. Axial short T1 inversion recovery (STIR) (A) and coronal postgadolinium fat-saturated T1-weighted (B) images through the face of a 17-year-old patient demonstrate an irregularly shaped mass (*large arrows*) that involves the central skull base, ethmoid region, and portions of the orbits with intracranial epidural extension (*small arrows*). A biopsy confirmed the diagnosis of alveolar rhabdomyosarcoma.

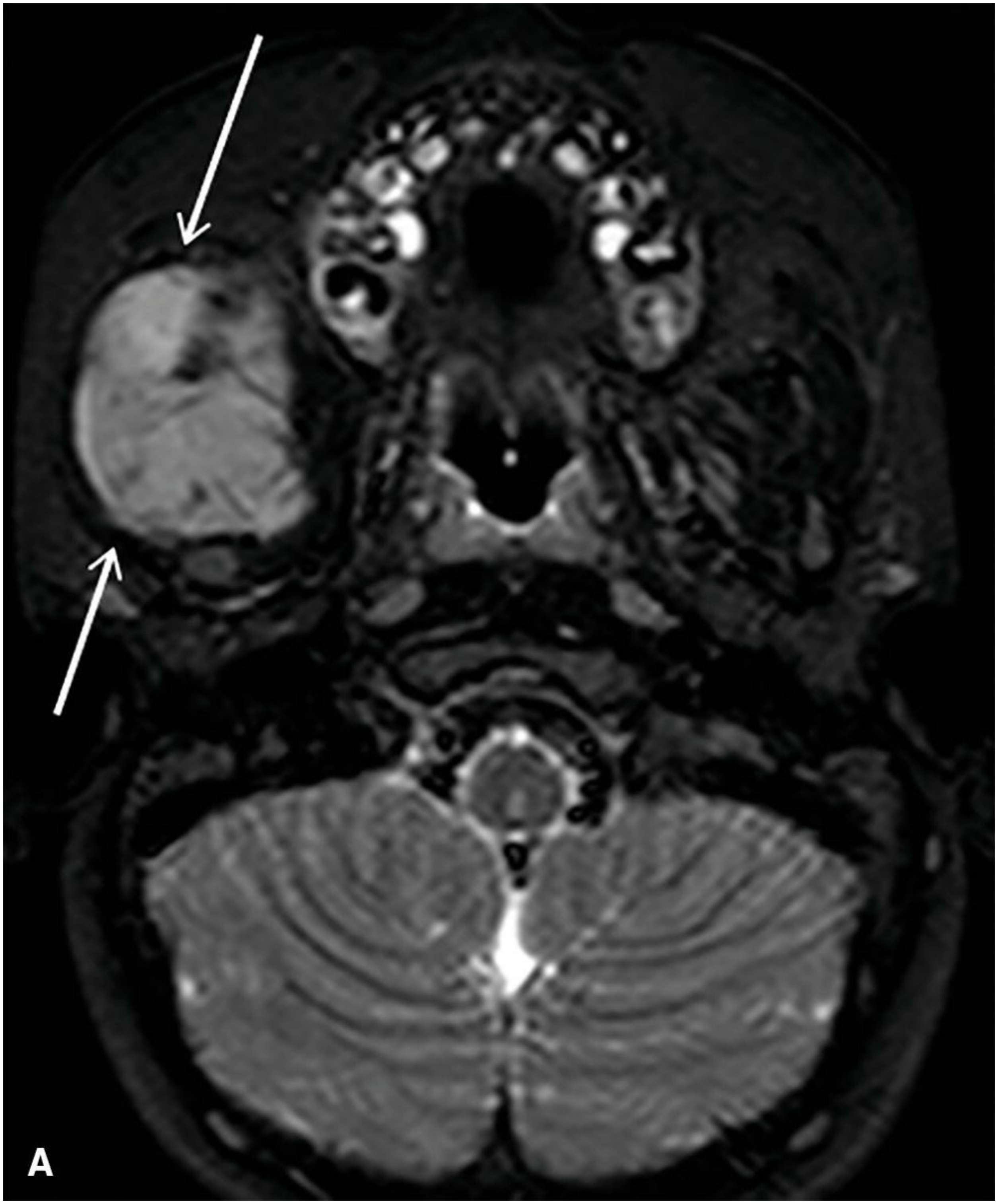
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Figure 24.2. Axial STIR (A) and axial (B) and coronal (C) postgadolinium fat-saturated T1-weighted images through the face of a 2-year-old child reveal a heterogeneous mass (*arrows*) involving the right masticator space. Biopsies of the mass demonstrated embryonal rhabdomyosarcoma.

A recent review of more than 1,600 children with rhabdomyosarcoma from 1991 to 2004 on intergroup studies suggested that staging procedures can be adapted in an algorithmic fashion based on presenting clinical factors, such that patients at low risk of distant metastatic disease—approximately one-third of patients—may be spared bone marrow studies and bone scans.[39]

In addition to standard cross-sectional imaging, PET-CT may also be a helpful adjunct to detect regional or distant metastatic disease, help evaluate therapeutic response, and identify patients who may benefit from therapy intensification for regional control.[40–42] Assessment of regional lymph nodes and potential biopsy where feasible may also guide management,[43] although neither PET scans or lymph node assessments are currently included as requirements in COG treatment protocols.

Comprehensive staging of rhabdomyosarcoma in children typically involves designating a stage (**Table 24.4**), a surgical–pathologic diagnosis, local tumor group (**Table 24.5**), and finally a risk group (**Table 24.6**).

Table 24.4 Children's Oncology Group: Pretreatment Staging System for Rhabdomyosarcoma

Stage	Sites of Primary Tumor	T Stage	Tumor Size	Regional Lymph Nodes	Distant Metastasis
1	Favorable site (Orbit; nonparameningeal head and neck; genitourinary tract other than kidney, bladder, and prostate; biliary tract)	T1 or T2	Any size	N0 or N1 or NX	M0
2	Unfavorable sites (any site other than favorable)	T1 or T2	a, ≤ 5 cm	N0 or NX	M0
3	Unfavorable sites (any site other than favorable)	T1 or T2	a, ≤ 5 cm b, > 5 cm	N1 N0 or N1 or NX	M0
4	Any site	T1 or T2	Any size	N0 or N1 or NX	M1

N0, absence of nodal spread; N1, presence of regional nodal spread beyond the primary site; X, unknown N status; M0, absence of metastatic spread; M1, presence of metastatic spread beyond the primary site and regional lymph nodes; T1, tumor confined to anatomic site of origin (noninvasive); T2a, tumor extension and/or fixation to surrounding tissue (invasive), tumor ≤5 cm in maximum diameter; T2b, tumor extension and/or fixation to surrounding tissue (invasive), tumor >5 cm in maximum diameter.From National Cancer Institute: PDQ® Childhood Rhabdomyosarcoma Treatment. 2014.

Table 24.5 Children's Oncology Group: Surgical–Pathologic Group Assignment System for Rhabdomyosarcoma

Group	Incidence	Definition
I	~13%	Localized tumor, completely removed with microscopically clear margins, and no regional lymph node involvement. Lymph node biopsy or sampling is encouraged if lymph nodes are clinically or radiographically suspicious.
II	~20%	Localized tumor, completely removed with (a) microscopic disease at the margin; (b) regional disease with involved, grossly removed regional lymph nodes without microresidual disease; **or** (c) regional disease with involved nodes, grossly removed but with microscopic residual and/or histologic involvement of the most distal node from the primary tumor
III	~48%	Localized tumor, incompletely removed with gross, residual disease after (a) biopsy only **or** (b) gross major resection of the primary tumor (>50%)
IV	~18%	Distant metastases are present at diagnosis. This category includes (a) radiographically identified evidence of tumor spread **and** (b) positive tumor cells in cerebral spinal fluid, pleural, or peritoneal fluids, or implants in these regions

From National Cancer Institute: PDQ® Childhood Rhabdomyosarcoma Treatment. 2014.

Table 24.6 Children's Oncology Group: Risk Group Classification for Rhabdomyosarcoma

Risk Group	Histology	Stage	Group
Low risk	Embryonal Embryonal	1 2, 3	I, II, III I, II
Intermediate risk	Embryonal Alveolar	2, 3 1, 2, 3	III I, II, III
High risk	Embryonal or alveolar	4	IV

From National Cancer Institute: PDQ® Childhood Rhabdomyosarcoma Treatment. 2014.

The nature and intensity of treatment, and subsequent outcomes, depend on appropriate staging and pathologic delineation of rhabdomyosarcomas, including tumor biology.

In comparison with children and adolescents with rhabdomyosarcoma, adult patients are more likely to present with disease in unfavorable primary sites, and exhibit pleomorphic histology, which is rarely seen in the pediatric population.[44]

Although the majority of cases of rhabdomyosarcoma are apparently sporadic in origin, reported associated familial and genetic conditions include Li-Fraumeni syndrome (with TP53 mutations), Costello syndrome,

Beckwith-Wiedemann syndrome, neurofibromatosis, and Noonan syndrome.[34,45] Additional studies are needed to evaluate the role of environmental factors, such as immune function and atopic exposure as potential protective factors in pediatric rhabdomyosarcoma.[46]

Standard chemotherapy consists typically of vincristine, actinomycin-D (also known as dactinomycin), and cyclophosphamide, in a regimen commonly known as VAC.[47] Additional agents have not convincingly altered the outcomes of this therapeutic backbone.[48] Focus continues to hone in on advancing cure rates while minimizing potential late effects of therapy. For patients who initially present with localized rhabdomyosarcoma, preventing local recurrence with surgery and/or radiotherapy remains vital.

Local therapy for rhabdomyosarcoma follows an approach of risk-adapted therapy with selection of modality (surgery vs. radiotherapy) designed to limit morbidity while optimizing local control. Maximal safe resection is performed at diagnosis when possible, followed by systemic therapy and additional local control measures including radiation therapy and additional surgery as determined by tumor histology, resectability, and the status of the surgical margins. Second-look surgery is an acceptable approach in order to balance outcome with toxicity. This approach enhances local control while minimizing long-term late effects. Defining appropriate patients for postoperative adjuvant radiotherapy remains somewhat controversial. Historically, patients have been selected for adjuvant radiotherapy based on histology (alveolar vs. embryonal). The basis for this approach derives from subset analyses of IRSG III to IV trials that have suggested no decrement to local control in children with alveolar rhabdomyosarcoma managed with surgery alone.[49]

Primary surgical resection can be considered prior to chemotherapy, but only if this would be safely achieved without adverse functional or cosmetic outcomes. Aggressive primary surgical approaches are not recommended, as attempts to debulk the tumor (with gross residual tumor) are not associated with improved outcomes compared to biopsy alone.[50] Particularly for head and neck rhabdomyosarcomas, typically only a biopsy is performed prior to chemotherapy; hence, most patients will have gross residual (group III) tumor and receive radiotherapy as primary means of local control.[36] Orbital rhabdomyosarcomas should be biopsied only; upfront exenteration should not

be performed, and later orbital exenteration should only be considered for those few patients with persistent or recurrent disease after chemotherapy and radiation therapy, which can achieve survival rates of 90% and above. For nonparameningeal and nonorbital rhabdomyosarcomas of the head and neck, such as those with superficial facial tumors, primary tumor excision (accepting narrow margins due to anatomy) and ipsilateral neck sampling of clinically concerning nodes can be considered.[8,51] Selected patients may be considered for second-look surgery to remove residual tumor (i.e., delayed primary excision) after initial therapy or in cases where this may modify the radiation dose required or have anticipated net positive impact on a given patient's functional outcome. The detection of viable tumor at the time of second-look surgery has not been found to impact overall survival.[49]

As only an estimated 15% of pediatric rhabdomyosarcoma patients have completely resected (group 1) disease, radiation therapy is included for local control in most cases.[36]

Recent data suggest the proton radiotherapy may be a comparably effective modality to photon radiotherapy for selected pediatric rhabdomyosarcoma patients, with future larger studies with sustained follow-up awaited to clarify whether it may indeed definitively reduce late effects.[52]

With modern therapy, typical survival rates for pediatric patients with rhabdomyosarcoma in the orbit are in the range of 90% or greater and 70% or greater for nonparameningeal head and neck rhabdomyosarcoma. Patients with parameningeal rhabdomyosarcoma are typically associated with poorer prognosis.[8,53] Cranial nerve palsies or skull base erosion is noted in approximately a third of children with parameningeal rhabdomyosarcoma and is associated with increased risk of recurrence. Urgent management typically includes earlier initiation of radiation therapy, with incomplete or longer-term clinical neurologic recovery from cranial nerve palsies possible.[8,54]

Generally, patients with recurrent and refractory rhabdomyosarcoma have a guarded long-term prognosis, but selected patients can achieve complete remission and more favorable 5-year survival rates with intensive salvage therapy, including those with initially localized presentation in favorable sites such as the orbit.[55,56]

Other Soft Tissue Sarcomas and Related Tumors

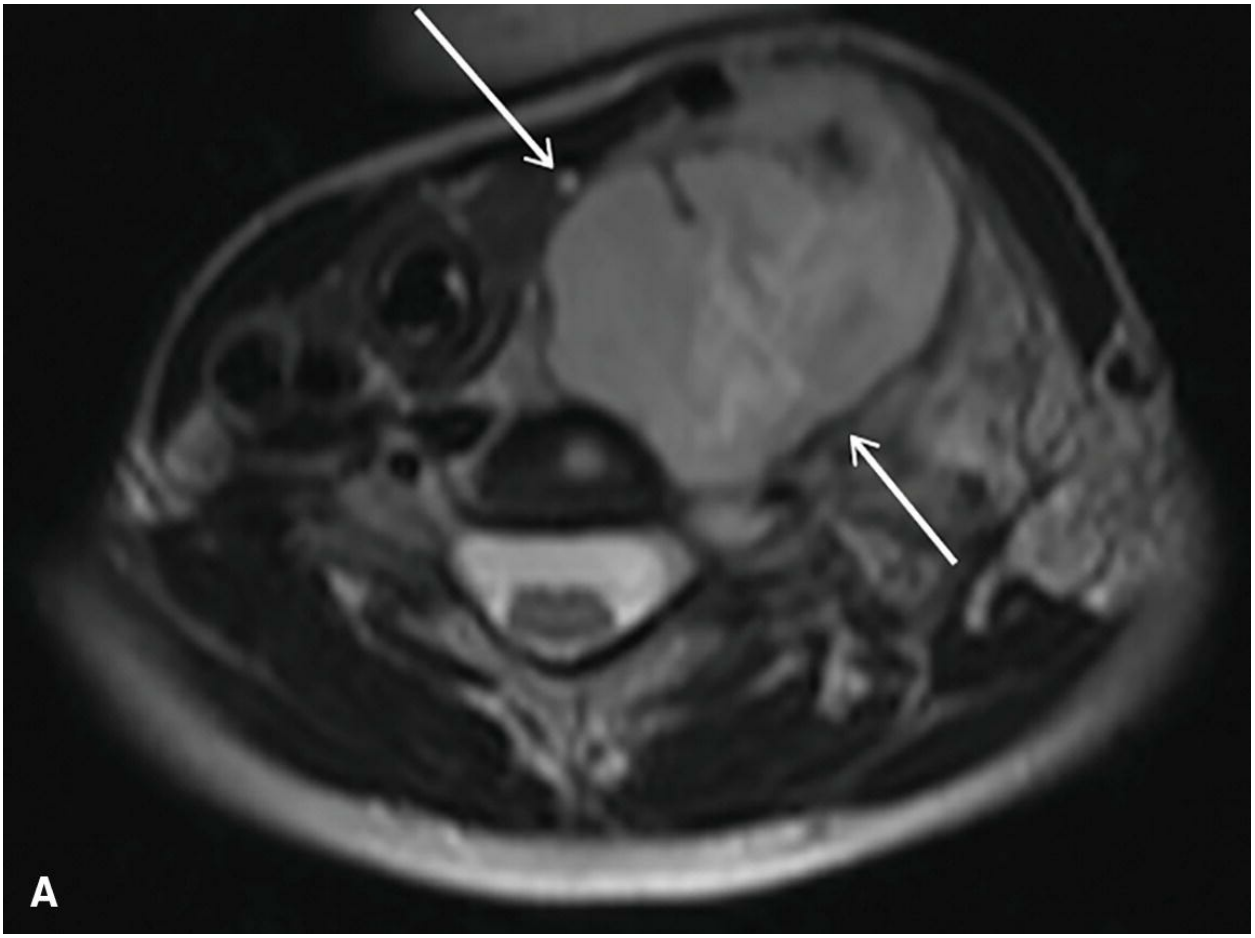
A number of soft tissue sarcomas constitute the varied group of sarcoma malignancies, apart from rhabdomyosarcoma, that can arise in the head and neck. The various nonrhabdomyosarcomatous soft tissue sarcomas (NRSTSs) altogether constitute <5% of pediatric malignancies; most pose challenges for local management, with infrequent lymph node or distant metastatic involvement.[57]

Synovial sarcoma is the most common NRSTS, with head and neck primary involvement in ~6%.[58] Synovial sarcomas are frequently small and, particularly when they present in the head and neck region, are often missed as a malignant entity due to its slow growth and well-circumscribed appearance.[59] Immunohistochemical staining typically demonstrates reduced INI1 nuclear reactivity, with a typical and specific chromosomal translocation, t(X;18)(p11.2;q11.2), associated with this diagnosis in 95% of cases, leading to rearrangement of the SYT gene (located on chromosome 18) with SSX1 or SSX2 (on chromosome X).[59] Better outcomes have generally been described among children than in adults, with SEER database analysis of 5-year survival estimates of 83% for children and adolescents and 62% for adults.[58] Typical management approaches are centered on surgical resection, with ongoing need for prospective data to definitively delineate the contribution of radiation therapy and chemotherapy.[59,60] Although various approaches have been used, a common chemotherapy regimen considered for NRSTSs selected for systemic therapy is doxorubicin with ifosfamide.[59,60]

In a recent analysis of the National Cancer Institute's SEER database, among 1,244 pediatric cases, MFH was among the most common diagnoses reported.[4] Whereas MFH is a common soft tissue sarcoma in adult patients, it has been inconsistently recognized and reported in the pediatric literature.[61,62] Although the nomenclature and classification of MFH and related tumors were revised by the World Health Organization in recent years, including in 1994 and 2002, studies reporting on MFH unfortunately have often aggregated MFH with other less aggressive subtypes, such as angiomatoid fibrous histiocytoma and plexiform fibrohistiocytic tumors,[61] with caution thus warranted in interpreting studies that may not have had the benefit of MFH as defined consistently on contemporary pathology review. One institutional retrospective study from 1971 to 2000 identified 28 patients

initially diagnosed with MFH, including 6 in the head and neck; 10 were reclassified as angiomatoid fibrous histiocytoma and one with plexiform fibrohistiocytic tumor; among the 17 patients with confirmed MFH, 5-year event-free survival is ~71%, compared to 100% for those reclassified with angiomatoid fibrous histiocytoma and plexiform fibrohistiocytic tumor. Wide local excision was favorably associated with event-free survival for localized tumors.[61]

Malignant peripheral nerve sheath tumors (MPNSTs) constitute another relatively common diagnosis within this rare group of pediatric head and neck NRSTSs.[57,63] A recent SEER analysis[64] demonstrated that in pediatric MPNST patients, the incidence was higher among adolescents; localized disease and surgical resection were positive prognostic factors, and median overall survival was only 30 months, consistent with other reports suggesting less favorable outcomes for MPNST among challenging NRSTS cases.[63] Unfortunately, MPNSTs often present with large tumors in axial locations, both of which are clinical factors reported to adversely impact outcome[63] (**Figs. 24.3** and **24.4**).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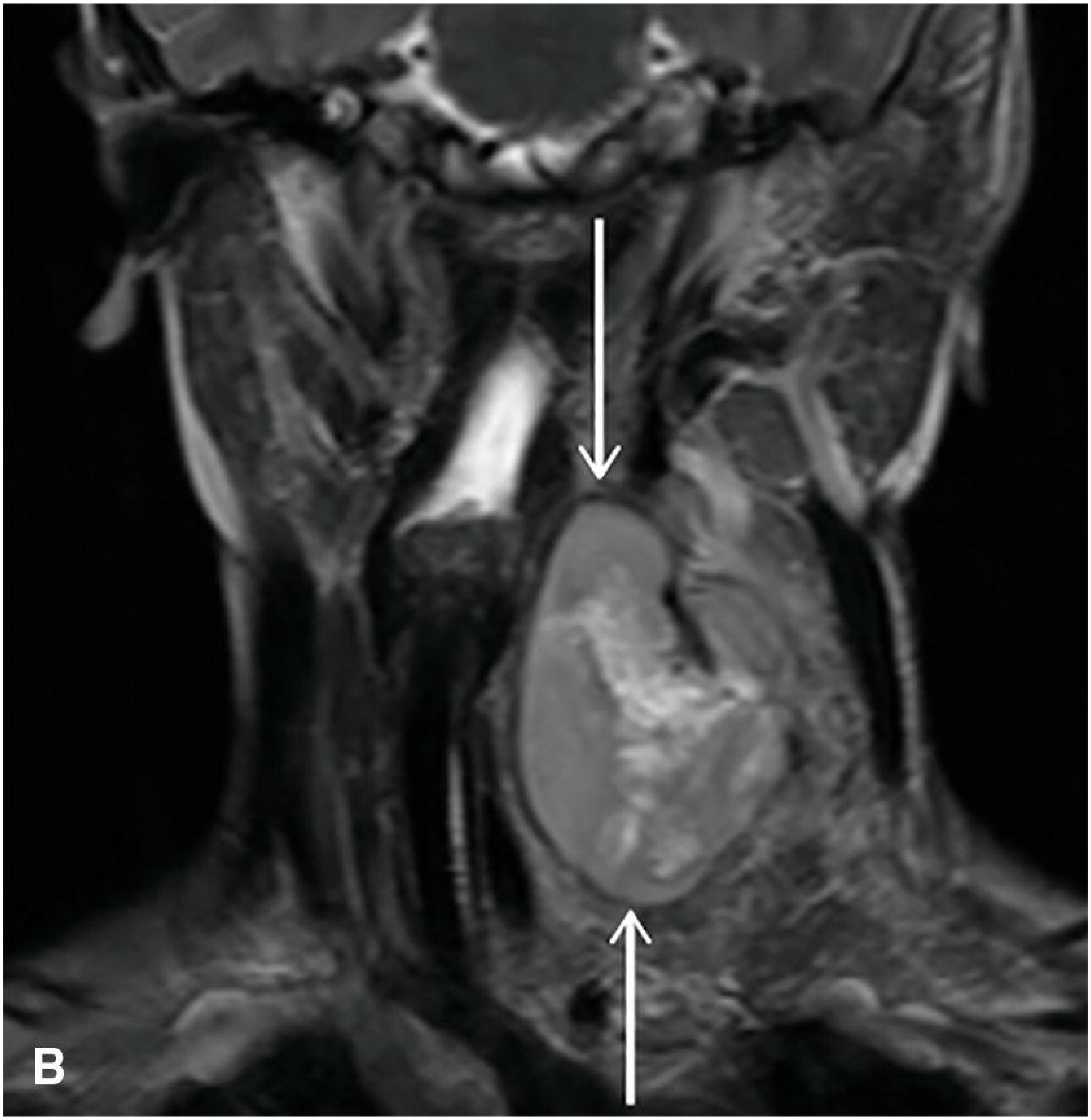
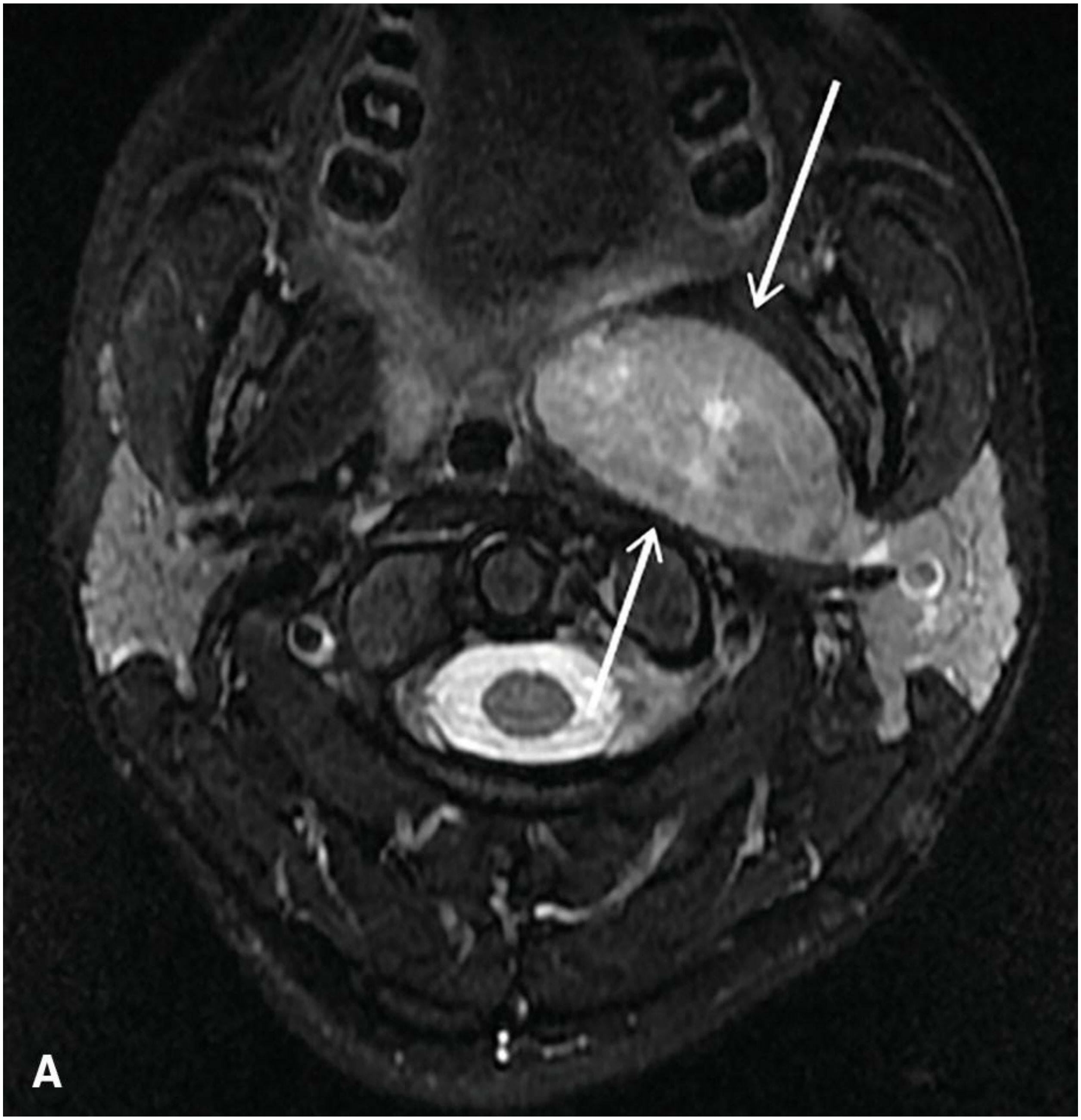


Figure 24.3. Axial **(A)** and coronal **(B)** T2-weighted images through the neck of a 7-year-old child show a heterogeneous, fairly well-marginated mass (*arrows*) involving the retrostyloid parapharyngeal space. The lesion was subtotally resected and found to be a malignant peripheral nerve sheath tumor (MPNST).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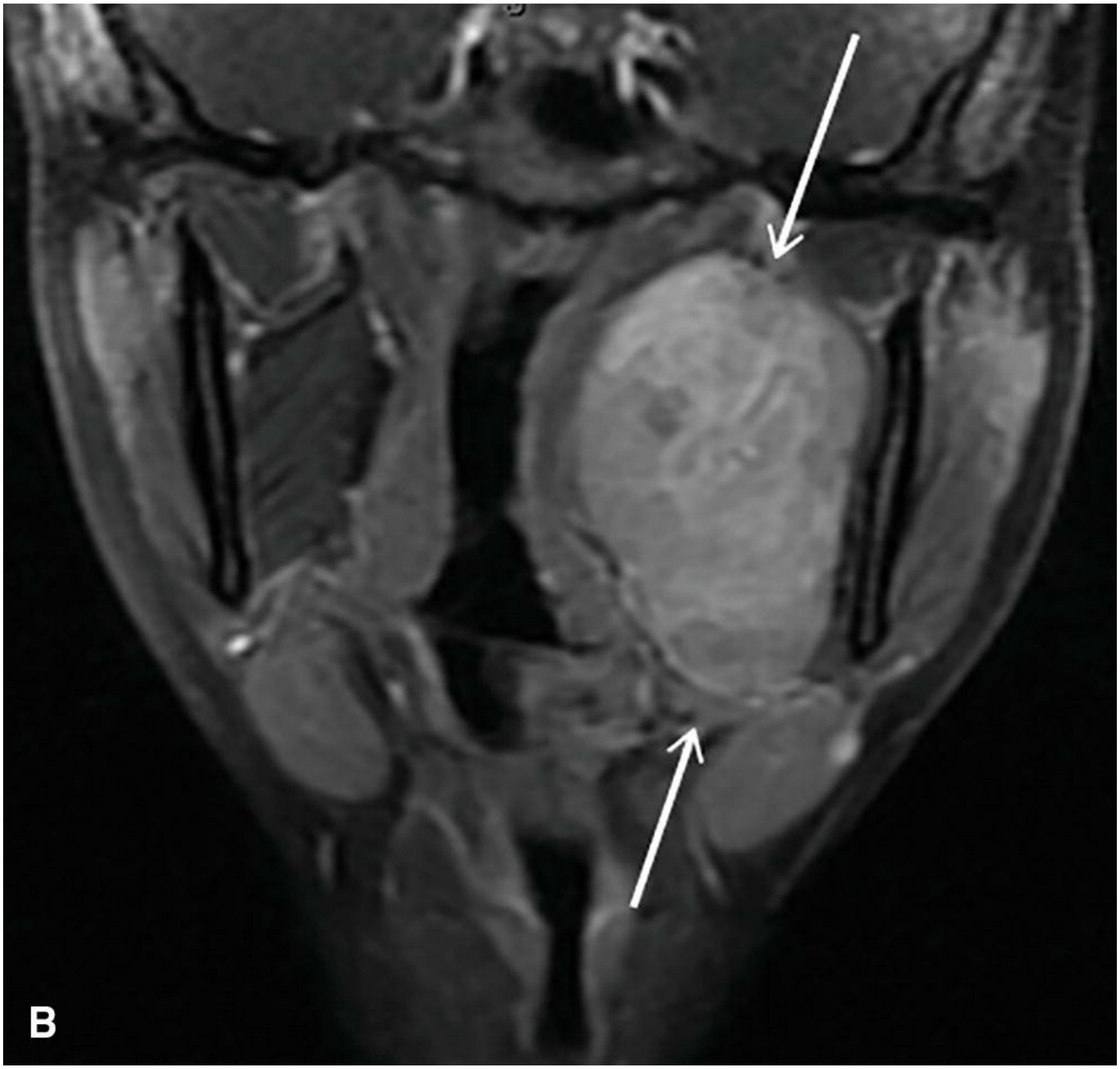


Figure 24.4. Axial fat-saturated T2-weighted **(A)** and coronal postgadolinium fat-saturated T1-weighted **(B)** images of the neck of a 27-year-old survivor of childhood neuroblastoma demonstrate a mildly heterogeneous well-defined mass in the left parapharyngeal space. The lesion was resected and determined to be an MPNST.

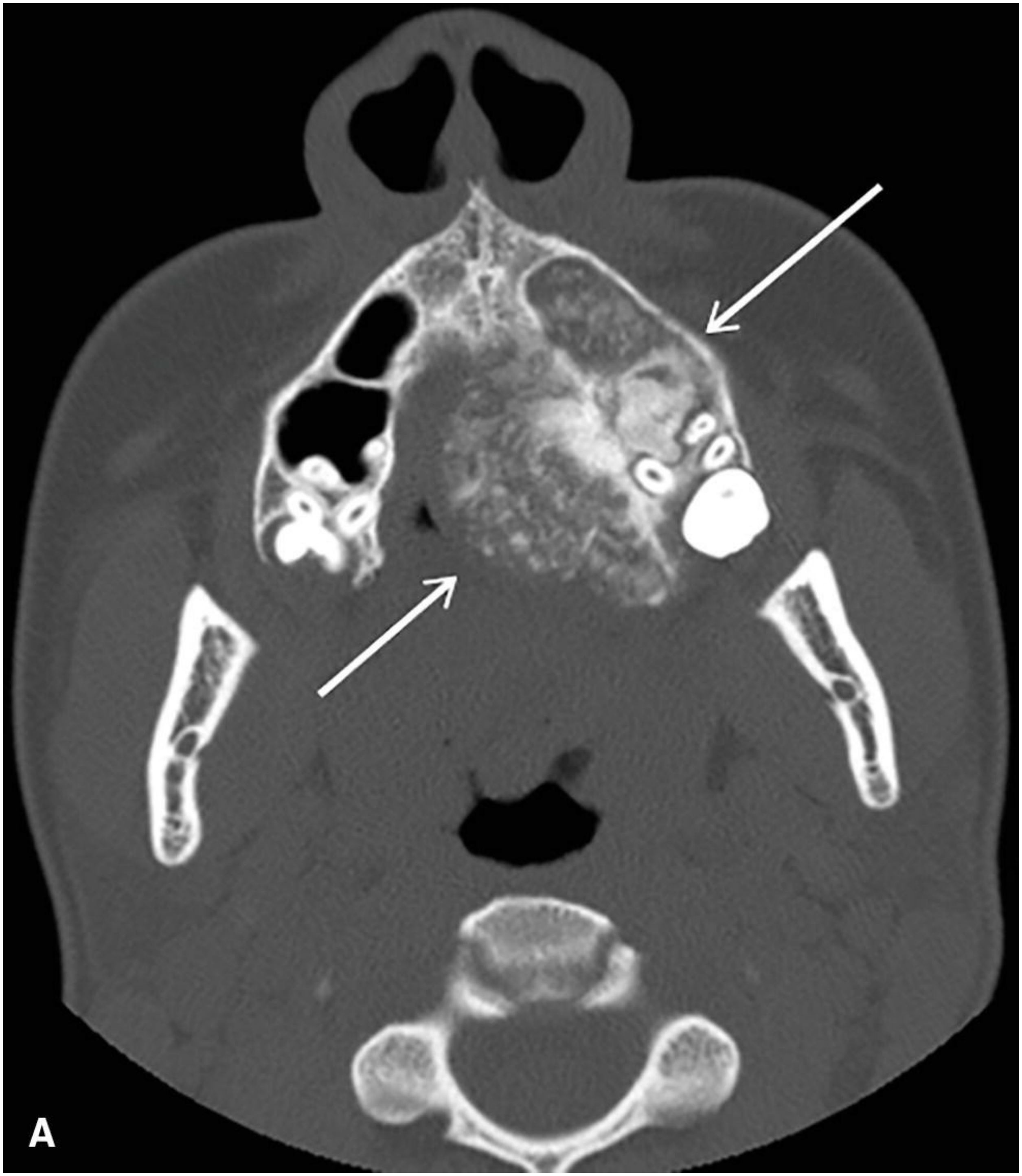
Other reported NRSTSs presenting in the head and neck in children and adolescents have included alveolar soft part sarcoma, epithelioid sarcoma, dermatofibrosarcoma protuberans, malignant hemangiopericytoma, leiomyosarcoma, fibrosarcoma, myofibroblastic sarcoma, inflammatory myofibroblastic tumor, and undifferentiated sarcoma.[8,57,62,63,65] Definitive

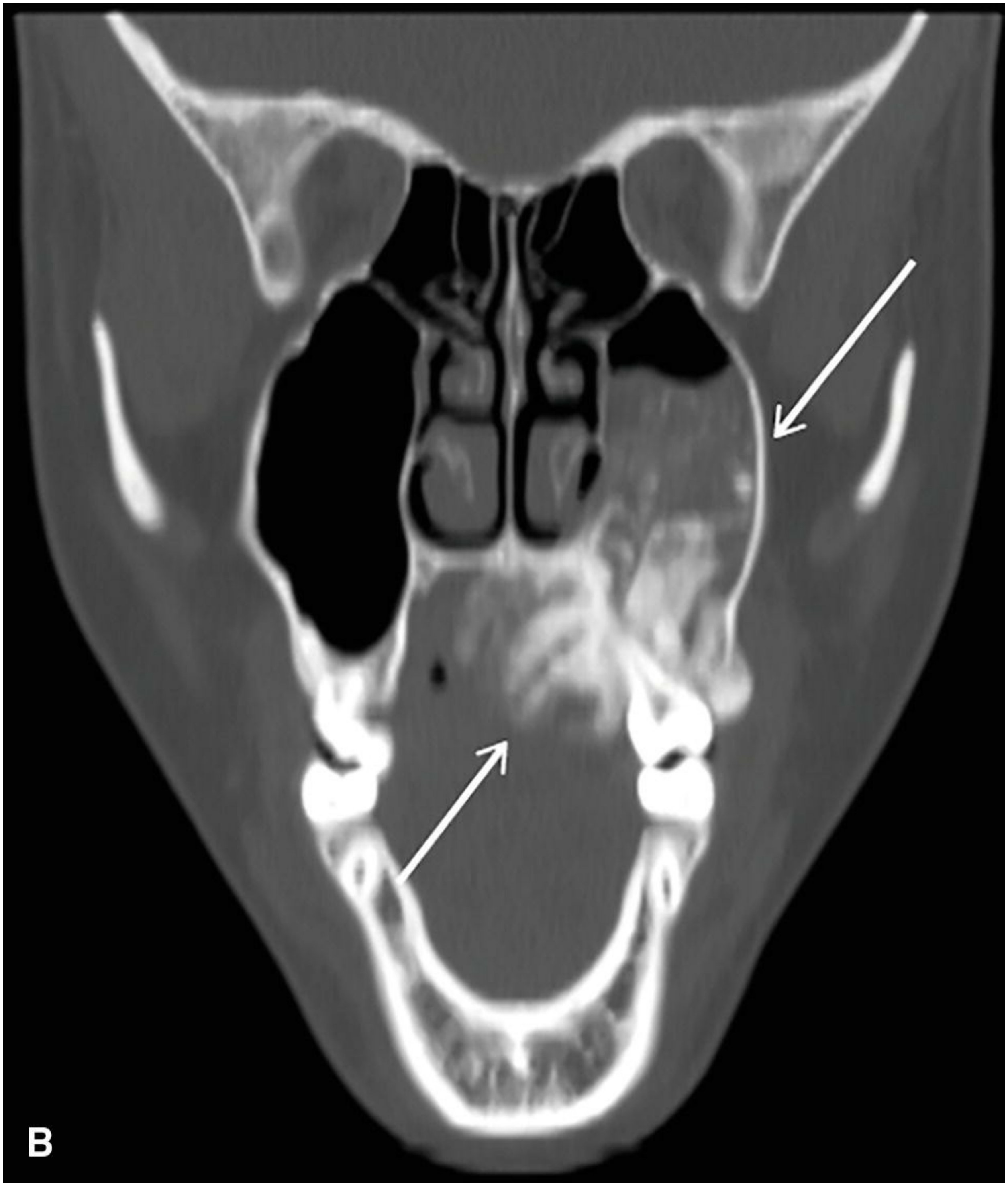
management is predicated on accurate diagnosis and coordinated multidisciplinary care. In the largest single-institutional retrospective review to date, Federico et al. described 58 pediatric and young adult patients with head and neck NRSTSs from 1964 to 2003.[57] Most patients were found to have small, high-grade tumors. Rates for event-free and overall survival at 10 years were 53% and 63% respectively. High grade, large size (>5 cm), invasiveness, and gross residual disease after surgery were associated with worse prognosis.[57] Novel approaches and further prospective data are needed to define optimal standardized management for children with NRSTSs.

Bone Sarcomas and Related Tumors

Pediatric bone sarcomas of the head and neck are generally rare and typically are localized at diagnosis.[66] Although osteosarcoma represents the most common pediatric bone sarcoma, only ~6% to 13% arise in the head and neck.[67] The maxilla and mandible are the most common sites and are also associated with better prognosis than are other, extragnathic sites in the head and neck.[67,68] Osteosarcomas in the head and neck appear distinct in a number of ways from the typical osteosarcoma that presents in the extremities, with variable histology, more often involving low or intermediate tumor grade, higher risk for local recurrence and less risk for distant metastatic disease compared to extremity osteosarcomas.[8,68] On CT scan, the tumor appears expansile with a prominent periosteal reaction and/or mineralization associated with osteoid tumor matrix[69] (**Fig. 24.5A and B**). MRI demonstrates a heterogeneous mass with low–signal intensity areas on both T1- and T2-weighted images, consistent with osseous lesion components, and intermediate- (T1-weighted) to high-signal (T2-weighted) tumor components that correspond to soft tissue (Fig. 24.5C and D). Complete surgical resection remains the foundation for improved failure-free and survival outcomes.[66,68] Prospective clinical data are warranted to better verify and define how prognostic factors, such as posttherapy tumor necrosis, as well as treatment approaches utilized for extremity osteosarcomas, including radiation therapy and chemotherapy, should be best interpreted and applied in head and neck osteosarcomas.[8,70] In addition to primary osteosarcoma, secondary osteosarcoma should be considered in older children or adolescents with a prior history of irradiation of the head and neck or prior hereditary retinoblastoma, with potential for similar outcomes as

those with primary osteosarcoma.[68]

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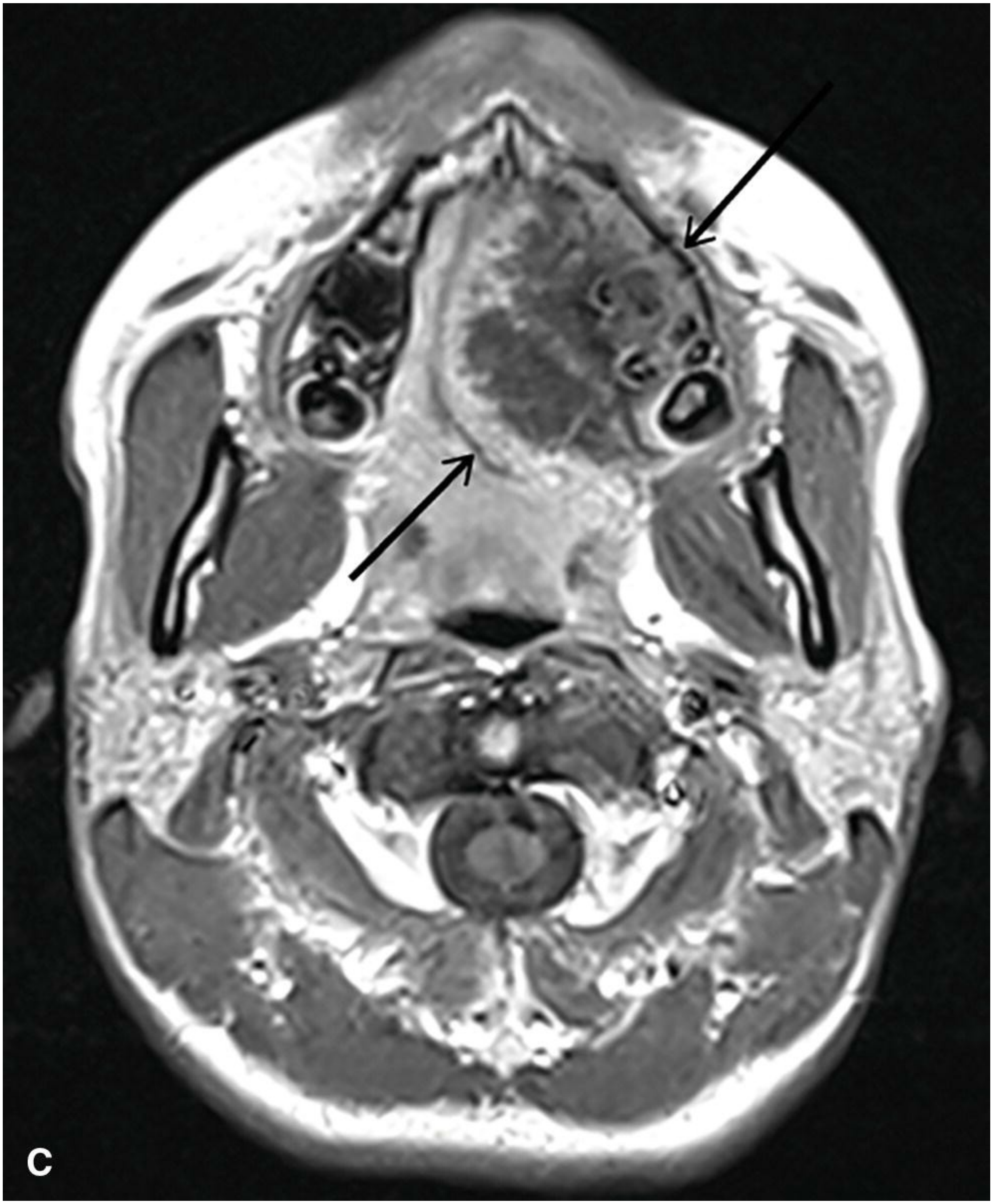
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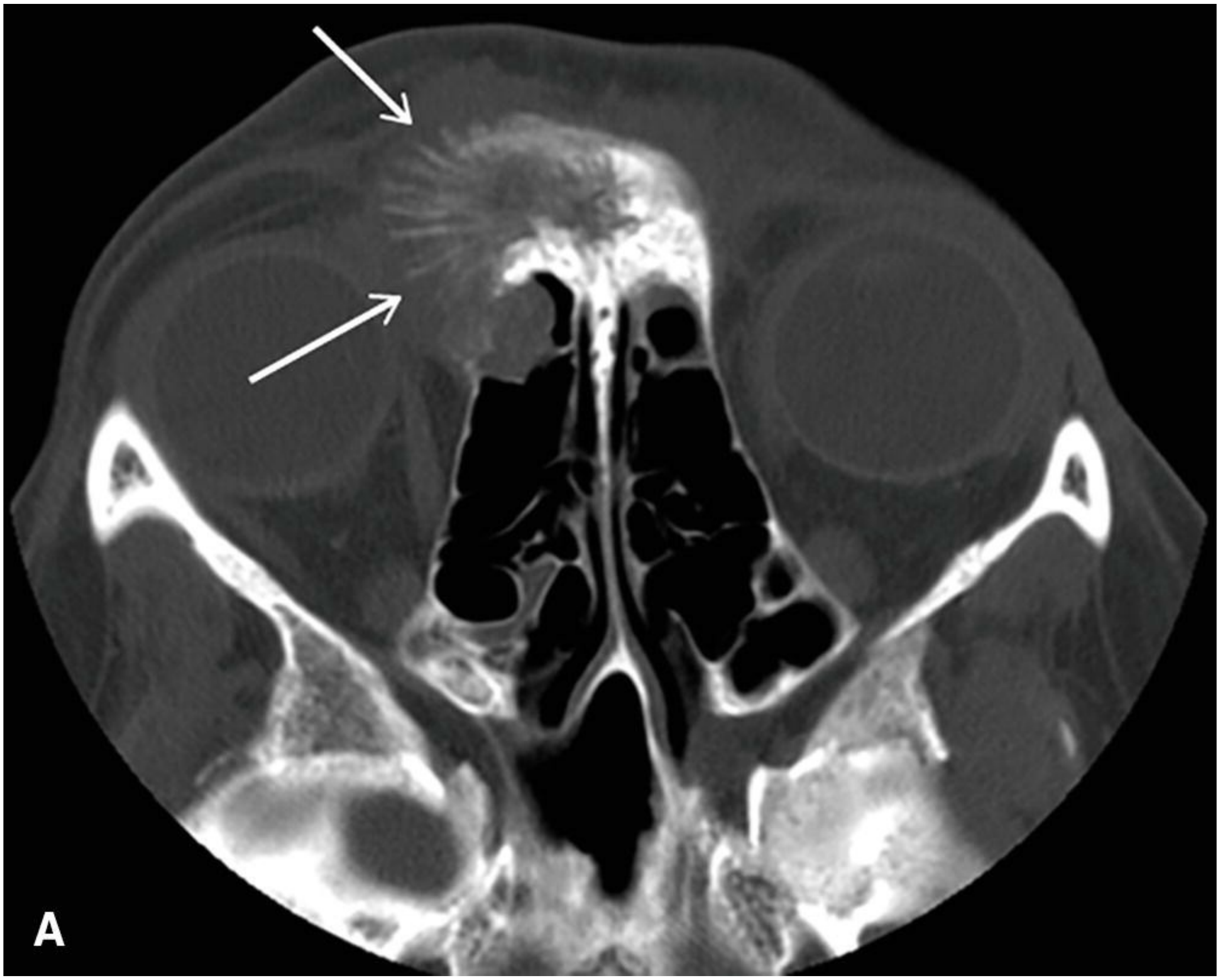
Figure 24.5. Axial **(A)** and coronal **(B)** noncontrast CT scan images of the maxillofacial region of a 14-year-old patient demonstrate an expansile,

destructive mass (*arrows*) in the left maxilla, including the left maxillary sinus, with a bony matrix. Axial **(C)** and coronal **(D)** postgadolinium T1-weighted images of the same patient's face show the mass (*arrows*) to contain a predominantly peripheral enhancing soft tissue component that surrounds low-signal internal osseous matrix and portions of the eroded maxilla and hard palate. Biopsy showed the lesion to be an osteosarcoma.

In addition to its presentation in the soft tissues, MFH can also develop less commonly as a primary bone tumor, most often involving the maxilla and mandible, and has been conventionally treated similar to osteosarcoma.[66,68]

Ewing sarcoma is the second most common pediatric bone sarcoma; similar to osteosarcoma, fewer than 10% of the cases involve the head and head region. The presentation of Ewing sarcoma in the head and neck is heterogeneous and can involve varied parts of the skull. Ewing sarcoma may also present in the soft tissues, cutaneously and subcutaneously, as extraosseous lesions constituting the established Ewing sarcoma family of tumors, with reported pediatric cases in the head and neck.[71] Ewing sarcoma has a variable imaging appearance, usually with aggressive characteristics.[72,73] CT scanning often demonstrates a destructive lesion with a "sunburst" or "hair-on-end" periosteal reaction (**Fig. 24.6A**). On MRI, the tumor may have a heterogeneous appearance with the "hair-on-end" periosteal reaction seen as low–signal intensity bands on T2-weighted images (Fig. 24.6B). Ewing sarcoma usually displays diffuse, heterogeneous enhancement (Fig. 24.6C and D). Systemic chemotherapy, coupled with surgery and/or radiation therapy, is typically a mainstay in management, with a less clearly defined role for aggressive surgery as compared to the use of surgery in the management of osteosarcoma or other bone sarcomas of the head and neck in children.[8,66]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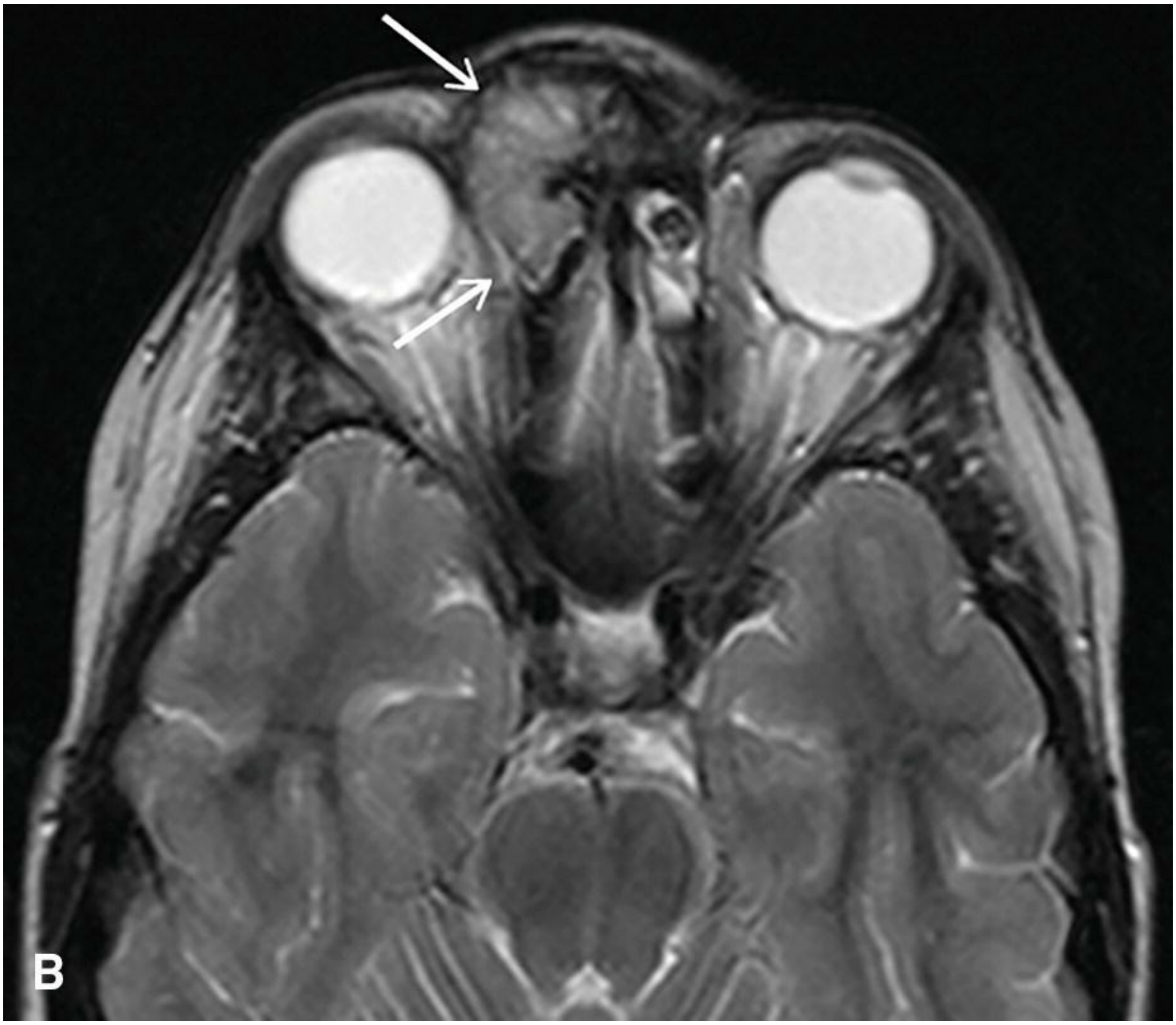
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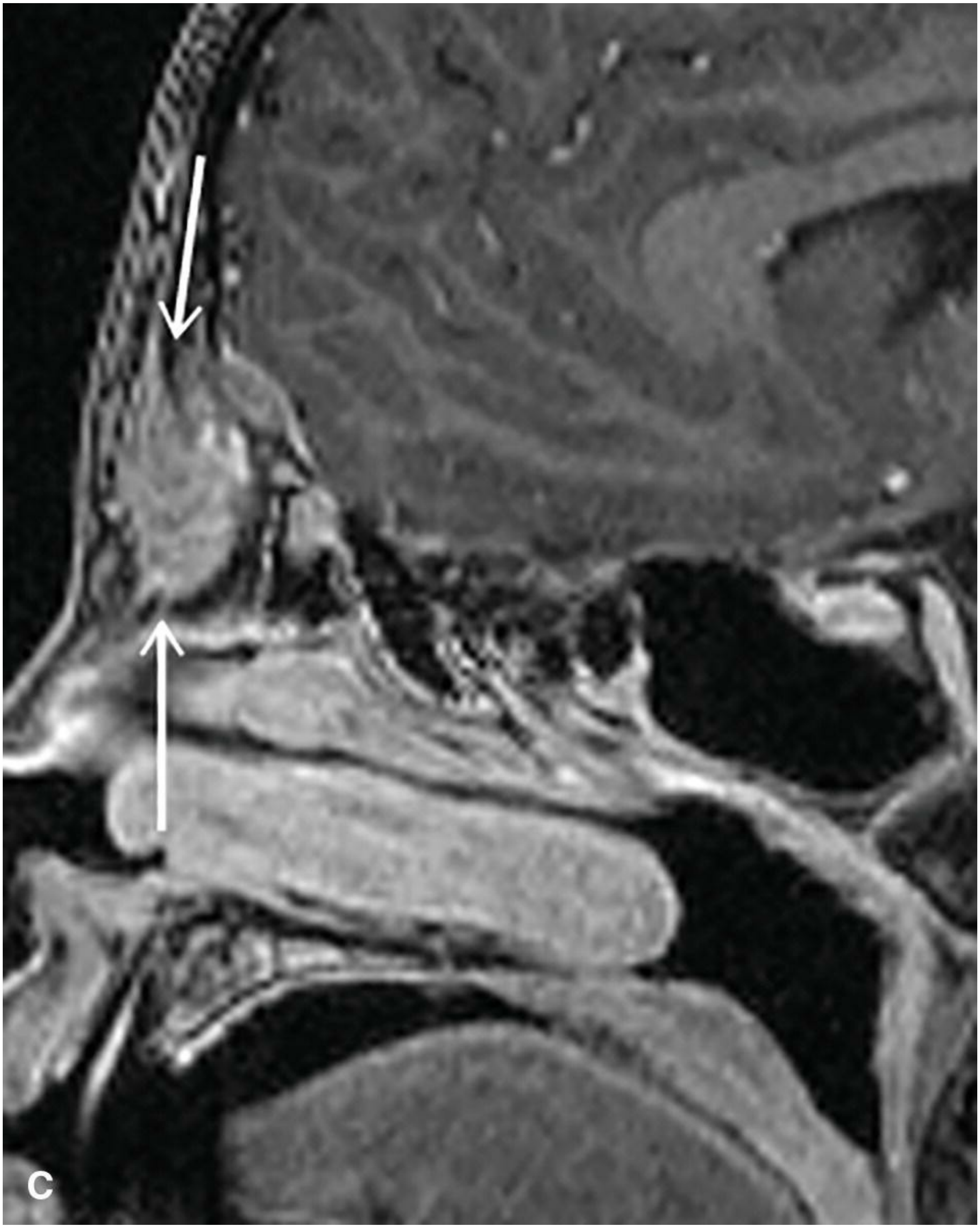
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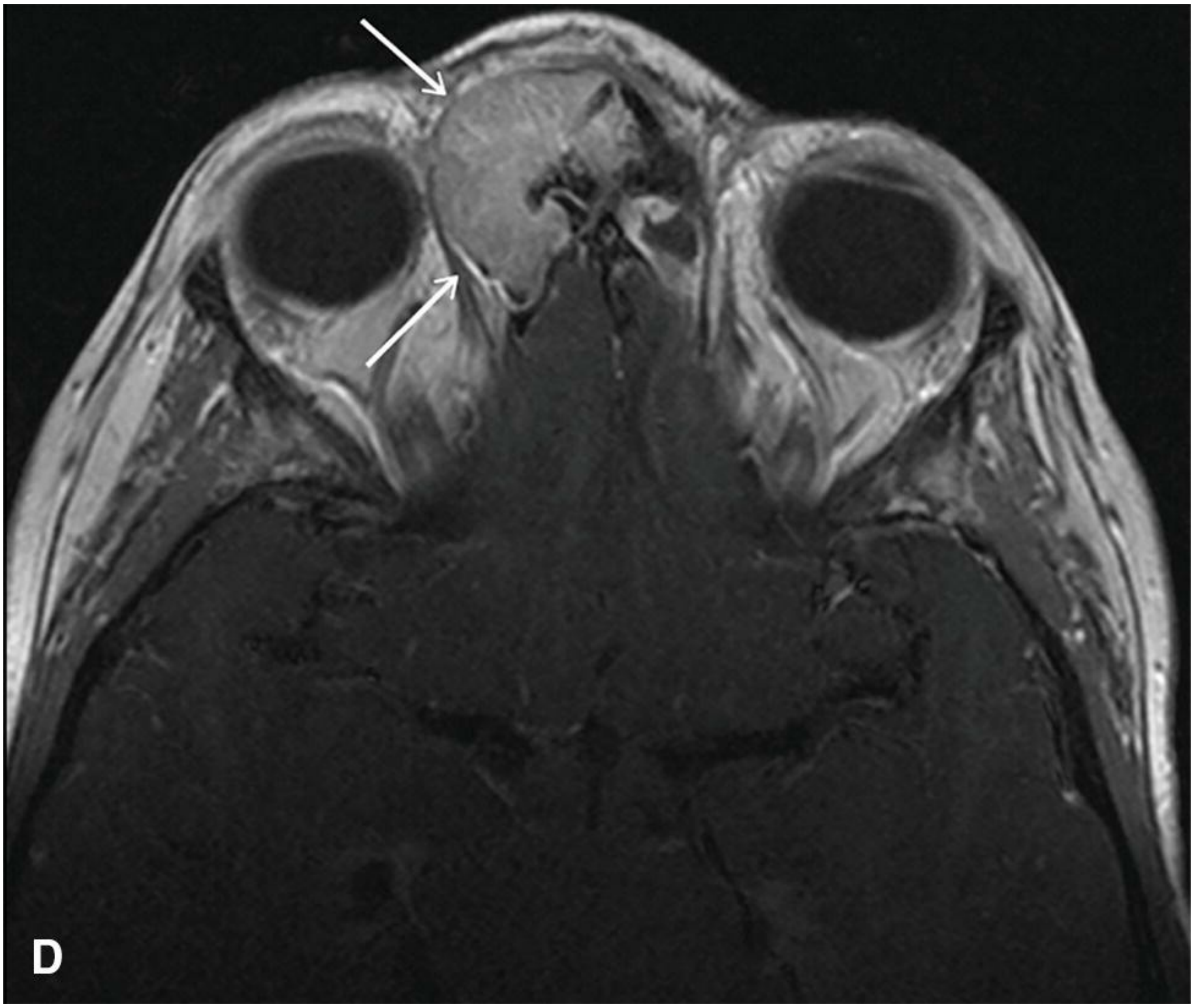
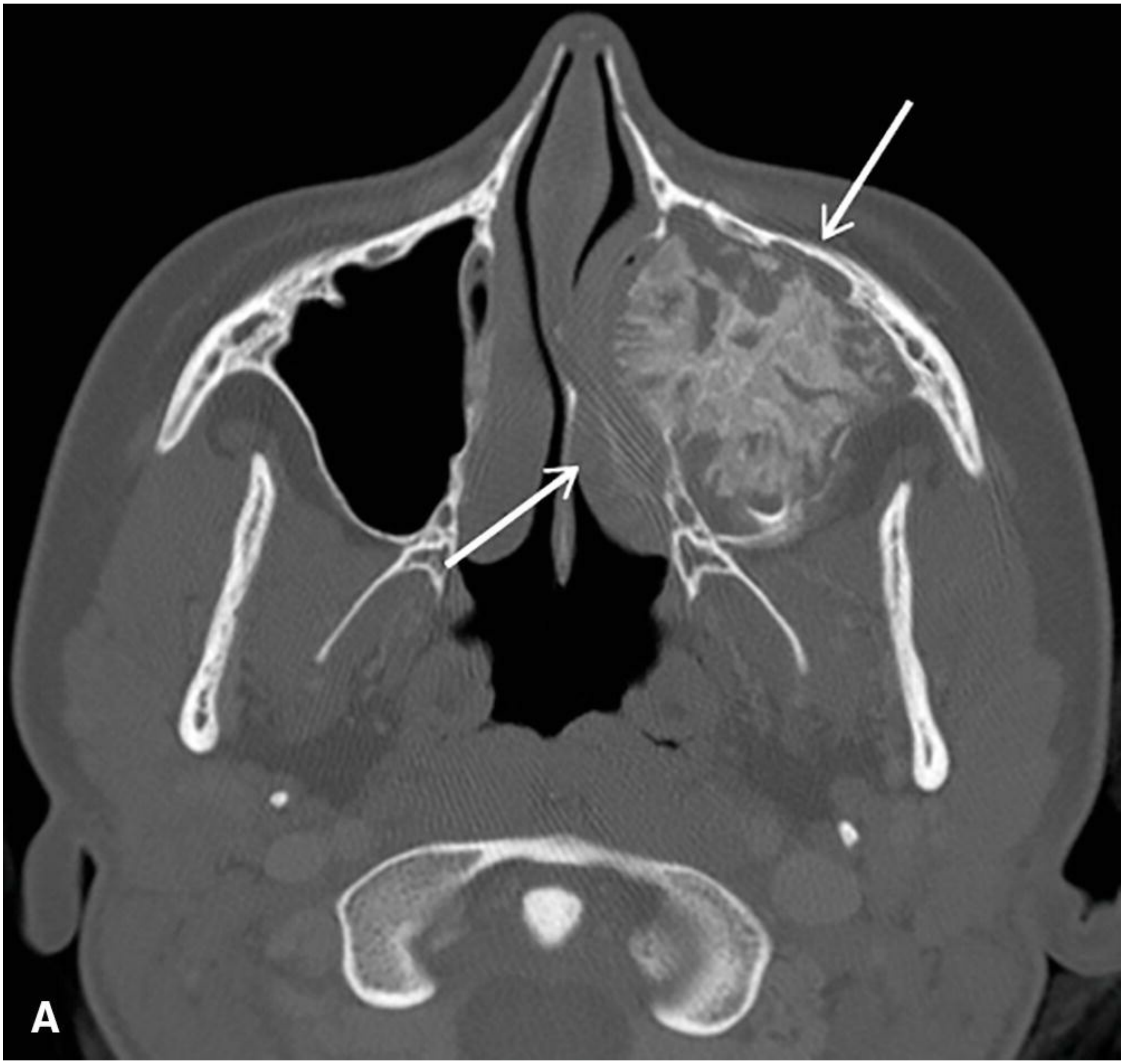
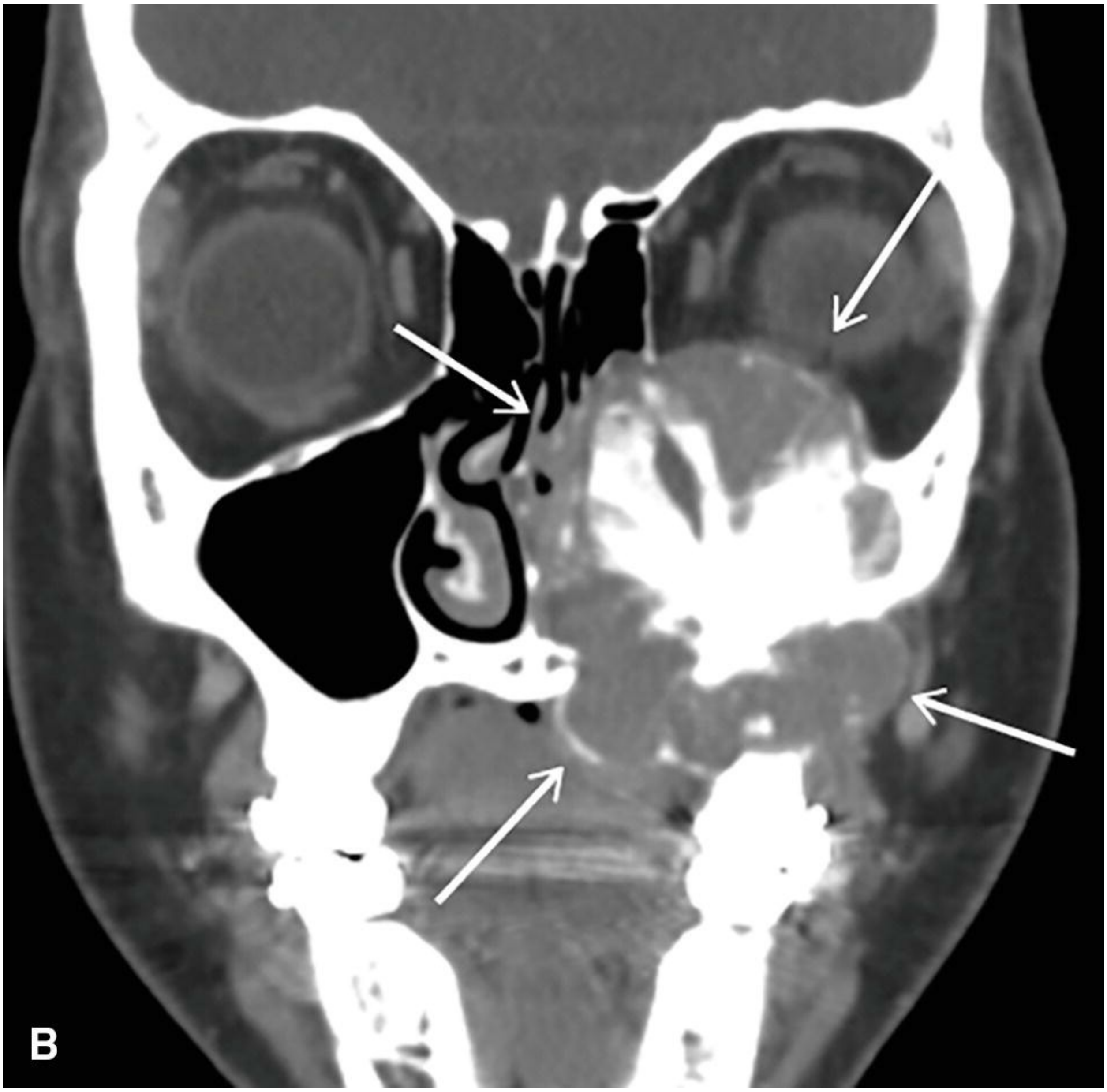


Figure 24.6. A: An axial CT scan image demonstrates a destructive lesion in the right orbitofrontal region of a 12-year-old child with a “hair-on-end” periosteal reaction (*arrows*). **B:** On axial T2-weighted image the “hair-on-end” spiculations appear as low–signal intensity bands that extend through predominantly high–signal intensity tumor (*arrows*). Sagittal **(C)** and axial **(D)** postgadolinium T1-weighted images reveal diffuse mildly heterogeneous enhancement within the mass. The lesion was resected and found to be Ewing sarcoma.

Chondrosarcoma can also occur in children and adolescents and is usually low grade, but can also include higher-grade and aggressive subtypes.[8] Chondrosarcoma has a varied appearance on imaging that may include coarse calcifications and destructive changes on CT scan, high signal intensity on T2-weighted MR images, low signal intensity on unenhanced

T1-weighted images, and variable enhancement[74,75] (**Fig. 24.7**). The mainstay of therapy is typically surgical resection, with exploration of radiation therapy and chemotherapy in selected cases.[8,76,77] Fibrosarcoma can also manifest as an uncommon pediatric primary bone tumor and is typically managed with wide surgical resection.[66] Overall, ongoing efforts are warranted to continue optimizing survival alongside functional and long-term outcomes for pediatric head and neck sarcomas.

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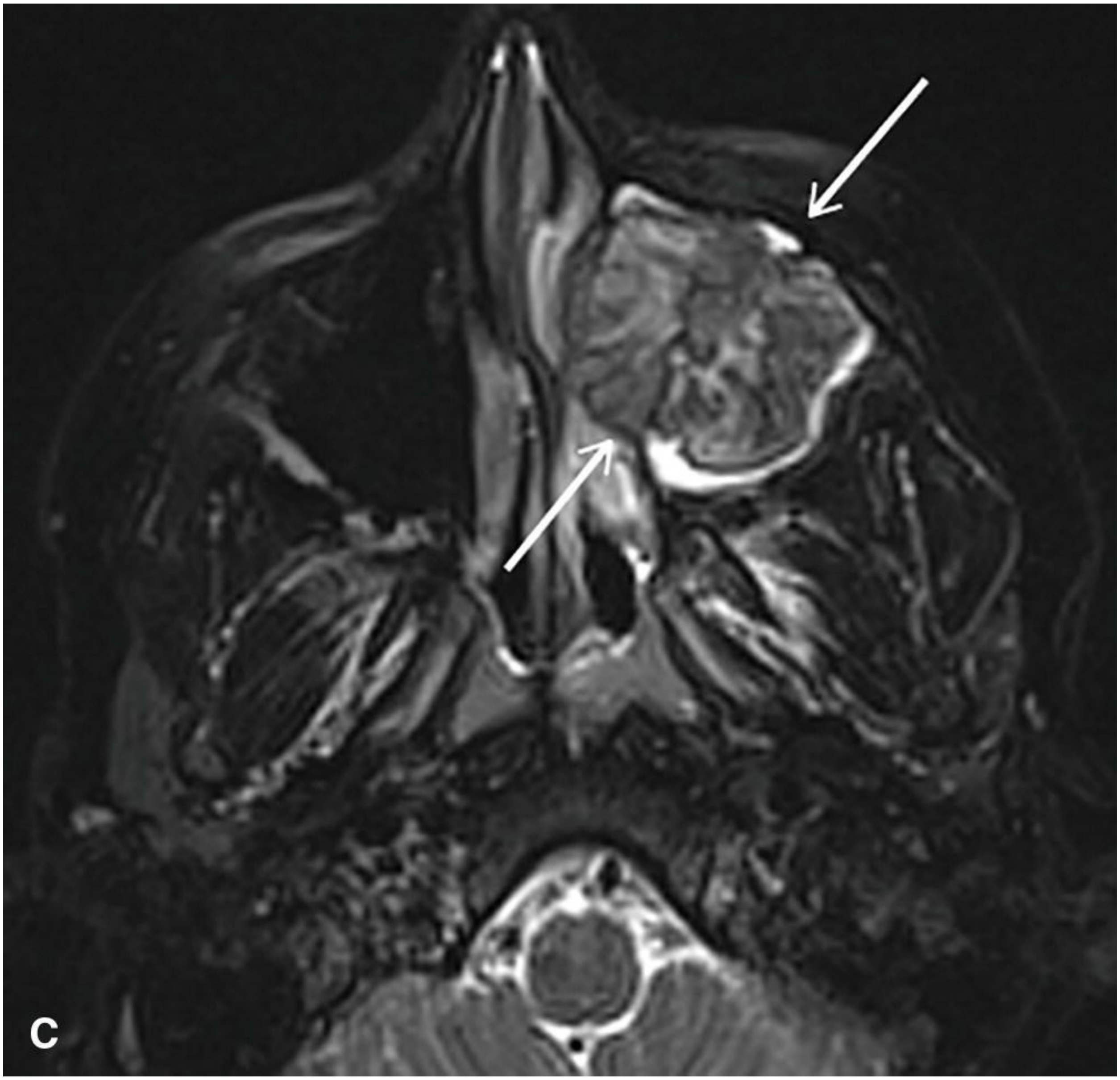
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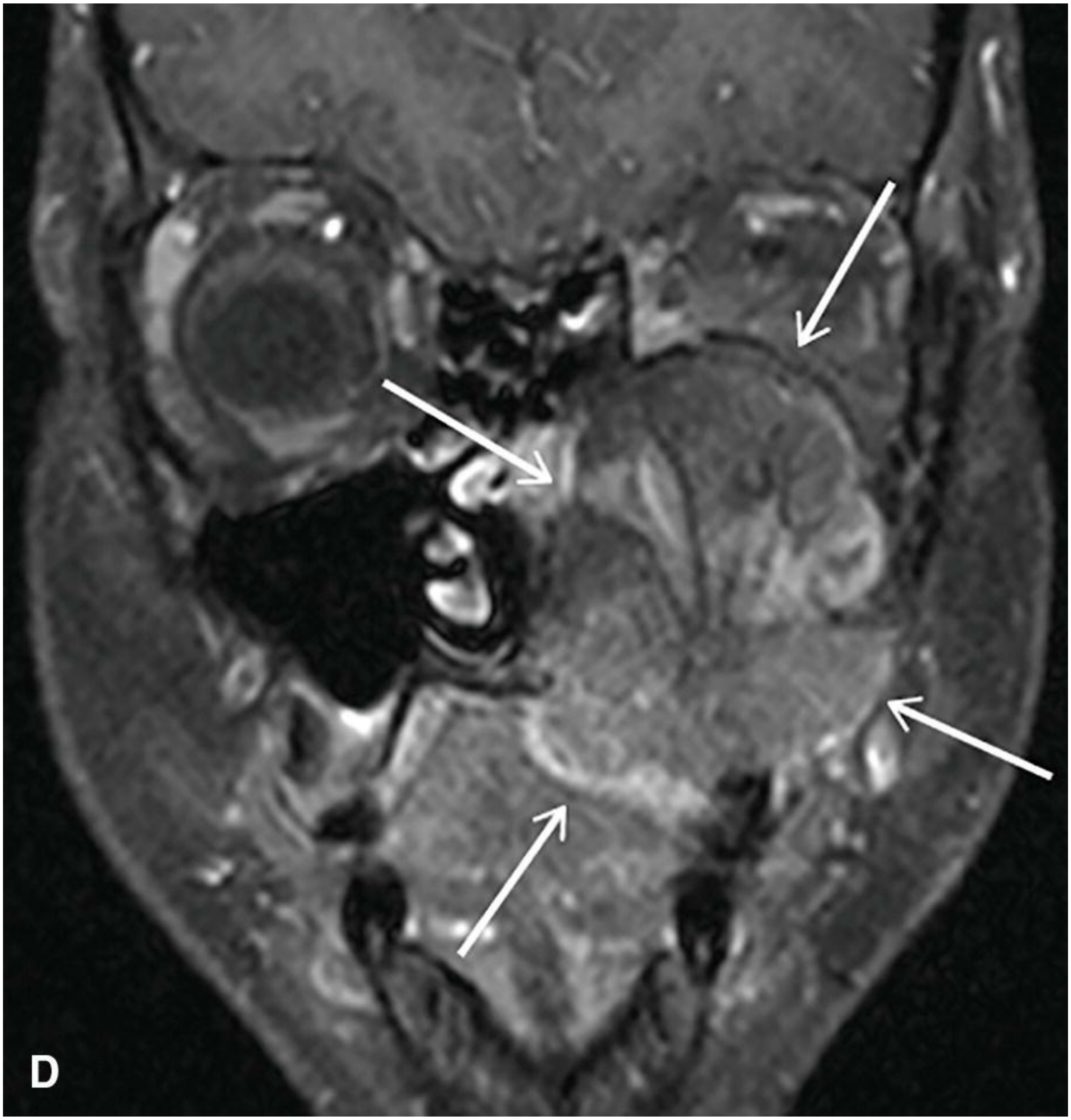

Figure 24.7. An axial CT scan image **(A)** with bone windows and a coronal CT scan image **(B)** with soft tissue windows reveal an erosive mass (*arrows*) centered in the left maxillary sinus of a 13-year-old patient that contains prominent coarse calcifications. The lesion extends into the left nasal cavity and left orbit and through the left side of the hard palate. **C:** A fat-saturated T2-weighted image demonstrates hyper- and hypointense areas within the mass (*arrows*) that correspond to noncalcified and calcified tumor components respectively. **D:** A postgadolinium fat-saturated coronal T1-weighted image shows heterogeneous enhancement of the tumor (arrows)

which, after resection, was determined to be a mesenchymal chondrosarcoma.


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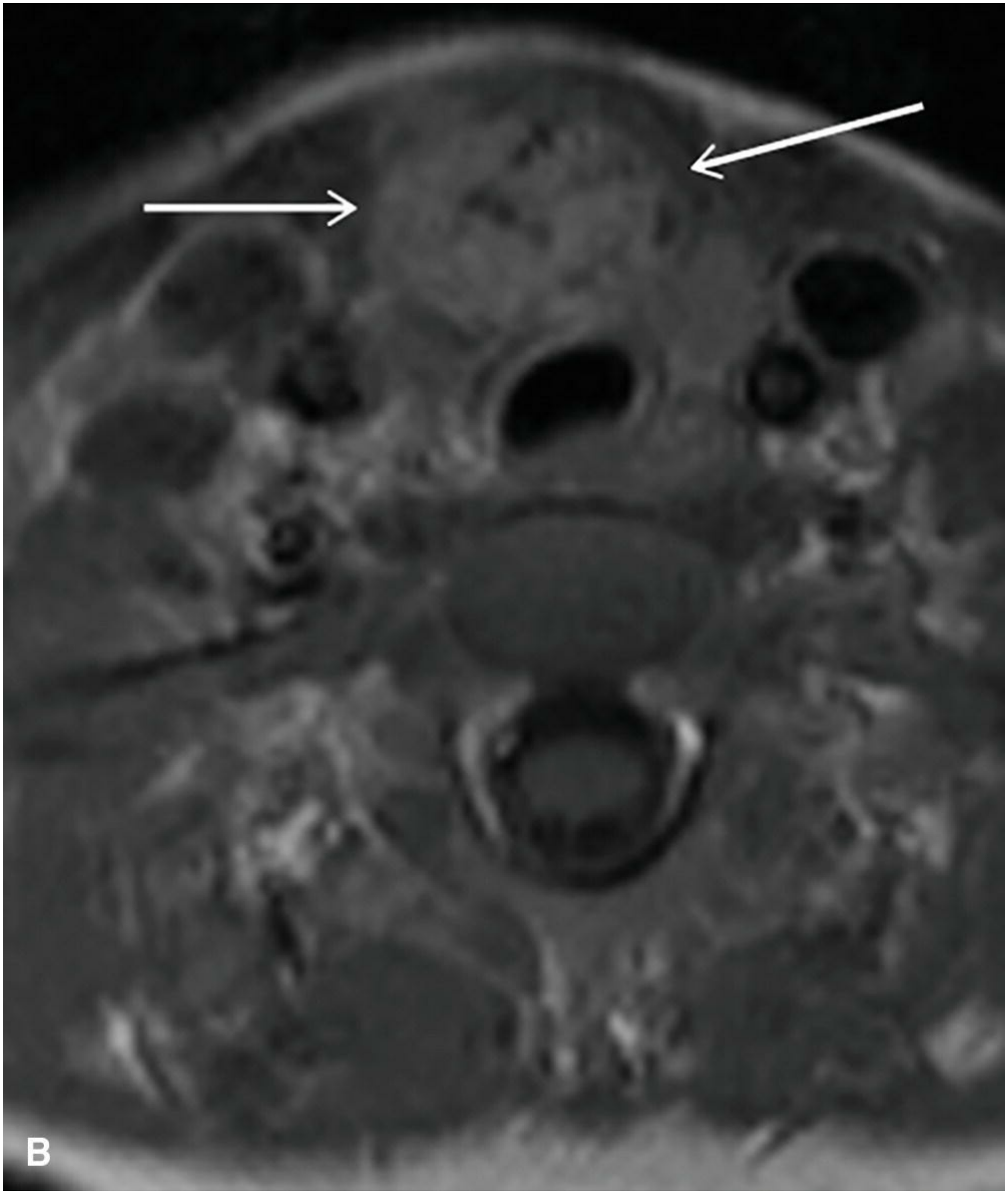

Figure 24.8. Axial T1-weighted **(A)** and postgadolinium T1-weighted **(B)** MRI images through the neck of a 3-year-old child demonstrate a mildly heterogeneous mass (*arrows*) anterior to the trachea. Almost all of the lesion enhances. Biopsy revealed a desmoid tumor.

Desmoid Tumors

Desmoid tumors (DT, also known as aggressive fibromatosis, desmoid-type fibromatosis, and musculoaponeurotic fibromatosis), first categorized in the 1960s, consist of a mesenchymal monoclonal proliferation that arises in musculoaponeurotic structures.[78,79] Incidence of 0.2 to 0.4 per 100,000 population has been reported with a relative peak incidence between puberty and age 40 years in women.[80] The incidence of childhood aggressive fibromatosis or pediatric desmoid tumors (PDT) peaks at about 8 years of age, with a range between birth and 19 years.[81,82] The broad histologic spectrum of DT falls between benign fibrous tissue proliferation and fibrosarcoma.[83] Although these tumors lack metastatic potential, they frequently recur locally owing to their capacity to infiltrate local tissues with a potential for significant local morbidity, even leading to death.[84] They also have a high incidence of recurrence after treatment, estimated between 24% and 77%. Two different types of DT are described: the isolated desmoid tumor and one seen in relationship with familial adenomatous polyposis/Gardner syndrome.[85,86] Interestingly, the progression of the tumor appears to be hormonally based, with regression occurring in females during menarche and menopause.[87]

Unlike their adult counterpart, data pertaining to PDT are sparse, and published reports suggest that pediatric desmoids may be particularly aggressive and difficult to control.[88,89] Recent data have emphasized the propensity of adult DT toward “biologic burnout.”[90,91] One recent study found that in 50% of adult patients affected by primary disease, and treated with observation only, progression did not occur by 5 years. Thus, a policy of initial observation has been advocated by some authors. Concurrent research has focused on the search for prognostic indicators for the purpose of patient risk stratification. Surgery has been considered the mainstay of treatment, with studies indicating that local recurrence rates after surgical resection range from 10% to 80%, when margins are negative or positive, respectively.[92,93] These data are in contrast to other adult studies reporting recurrence rates from 30% to 50%, regardless of margin status.[94] The pathogenesis of DT likely represents a “field effect,” whereby subclinical spread is not detectable at the time of extirpation. The role of radiation therapy in the management of adult DT is controversial.[95,96] Many studies

have demonstrated durable local control in patients with marginally resectable or unresectable tumors treated definitively with radiation therapy. Radiation doses of 50 to 60 Gy achieve local control in 70% to 80% of adults treated for gross residual disease and may improve recurrence-free survival (RFS) compared with surgery alone; however, results in children are controversial. Chemotherapy may be used for tumors that are unresectable, recurrent, or whose surgical removal would result in significant morbidity.[95]–[99] Tumor size has not been found to consistently predict outcome, given that desmoid behavior is likely ultimately determined by multiple factors.[100] The anatomic site of the primary tumor can influence treatment strategies, particularly in prepubertal children for whom effects of surgery and radiation on growth and development must be considered.

On CT scan, desmoid tumors are often poorly defined and may erode adjacent bone. They have a variable appearance on T1-weighted MRI and may appear bright with small areas of low signal intensity on T2-weighted imaging. Following gadolinium contrast administration, desmoid tumors usually demonstrate diffuse or peripheral enhancement (**Fig. 24.8**).[101]

In a recent study from St. Jude Children’s Hospital, 39 patients with PDT, of whom 8 (21%) arose in the head and neck, were treated over a 12-year period. In the entire series, only 18% of patients had microscopically negative margins.[102] RFS at 5 years was 73.1%. Factors associated with decreased RFS were patient age >12 years, and tumor size >5 cm. Margin status did not affect RFS, and the selective use of radiation therapy appeared to improve RFS. Although most defects could be closed primarily, head and neck defects, in particular, more frequently required flap closure. Similarly, long-term issues with appearance, facial nerve function, and functional outcomes including dental rehabilitation were more common in lesions in the head and neck.

Hodgkin Lymphoma

HL is a malignancy of the lymphoreticular system that most often affects adolescents and young adults. HL is uncommon in preadolescent children and is rarely seen in children younger than 5 years. Initial attempts to treat HL were based on the use of radiotherapy alone by René Gilbert in the early 1920s, who first treated adjacent lymph node regions electively in patients

with classical HL. The trend of delivering low-dose irradiation to sites with gross disease remained standard for many years, until the advent of effective systemic chemotherapy. In the interim, Henry Kaplan and Saul Rosenberg helped to optimize survival outcomes with radiotherapy. Since approximately the 1980s, the clinical approach has been to treat children with classical HL with chemotherapy followed by radiotherapy or with chemotherapy alone as was established in children diagnosed with favorable stage IA or IIA disease.[103,104] In children with favorable classical HL, the early response to multiagent chemotherapy (~2 months) is used to determine whether radiotherapeutic consolidation is required, thus allowing some proportion of children to be managed without radiotherapy at all.[105] In children with unfavorable early-stage, classical HL, multiagent chemotherapy is followed by involved-nodal or modified involved-field radiotherapy to 21 to 25.5 Gy. Children with advanced-stage, classical HL, regardless of bulk, receive multiagent chemotherapy followed by involved-field radiotherapy to sites of initial disease. The combined modality approach seeks to reduce toxicities from either intervention, while maximizing cure rates. Radiation volumes have been slowly shrinking and, in many instances, no longer include classical involved fields, which reflects a growing respect for the increased efficacy of current systemic therapies.

HL arises within lymph nodes in more than 90% of childhood cases. Extranodal primary sites are rare, but systemic involvement does occur with progression of the disease. The spleen is the most common extranodal site for HL, with the liver and lymph nodes in the abdomen and retroperitoneum also being common sites.[106,107] Mediastinal lymph node involvement is common, particularly in association with right supraclavicular cervical disease.[108] Pulmonary involvement is often due to extranodal spread from contiguous mediastinal and hilar lymph nodes.[109] In contrast, bone and bone marrow involvement arise from hematogenous spread.[110] One-third of children with HL have nonspecific systemic symptoms at the time of presentation; these so-called B symptoms include unexplained fever, night sweats, and unintended weight loss.[108]

HL is distinguished morphologically from non-Hodgkin lymphoma by the diagnostic presence of Reed-Sternberg cells. Reed-Sternberg cells are binucleate or multinucleate giant cells with a clear halo zone around the nucleolus; they are suspected to be of B-cell lineage.[108,111] The historically

used Rye classification system recognizes four such subtypes: (1) lymphocyte predominance, (2) nodular sclerosis, (3) mixed cellularity, and (4) lymphocyte depletion.[112] Overall, about two-thirds of children have nodular sclerosis HL at the time of presentation; the lymphocyte predominance and mixed cellularity subtypes are relatively more common in children 10 years of age and younger.[113]

These histopathologic HL subtypes have prognostic implications.[114] Lymphocyte predominant HL has the most favorable prognosis, with poorer survival (in prognostic order) associated with nodular sclerosis, mixed cellularity, and lymphocyte-depleted HL.[114] The more recent Revised European-American Lymphoma (REAL) classification separates HL into classic HL and nodular lymphocyte predominant HL (NLPHL)[115] (Harris NL 1994). This system is based on the observation that NLPHL is clinically less aggressive than the other subtypes that constitute classic HL, with NLPHL having a decreased incidence of B symptoms and mediastinal involvement, as well as typically presenting at an earlier stage.[115]

The vast majority of patients with cervicofacial HL have disease outside of the head and neck region at presentation, and the diagnosis is established by lymph node biopsy. Although fine needle aspiration biopsy has been used to diagnose HL by the identification of Reed-Sternberg cells,[116] open excisional biopsy is recommended in newly diagnosed cases for adequate tissue sampling.

It is essential that the full extent of the disease be defined in each patient before specific treatment is instituted. The Rye symposium, held in 1965, provided an anatomic breakdown by lymph node groups for staging purposes. This was superseded in 1970 by the Ann Arbor staging system, or a modification thereof,[117] which is presently in use (see **Tables 24.7 and 24.8**). The Ann Arbor staging system recognizes the fact that HL spreads via lymphatics in a contiguous fashion and can involve extralymphatic sites. The involvement of extranodal sites in HL is designated by E. The presence or absence of B symptoms is designated by B or A, respectively. Cotswold staging classification addresses patients with bulky disease.

Table 24.7 Rye Symposium Lymph Node Staging (1965)

a. Waldeyer ring
b. Preauricular, occipital, cervical, and supraclavicular
c. Infraclavicular
d. Mediastinal
e. Hilar
f. Axillary and pectoral
g. Epitrochlear and brachial
h. Spleen
i. Para-aortic
j. Mesenteric
k. Iliac
l. Inguinal and femoral
m. Popliteal

Table 24.8 Ann Arbor Staging System (1970)

Stage	Description
I	Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an extralymphatic organ or site (III_E), by involvement of the spleen (III_S), or both (III_{E+S})
IV	Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

Clinical staging includes history, physical examination, radiographic studies, and laboratory tests in addition to biopsy. Chest radiography with anteroposterior and lateral views may be required for the assessment of airway patency or bulk of disease; masses that occupy more than one-third of the thoracic diameter are associated with a poor prognosis (Roskos 1982, Robinson 1984). CT of the neck and chest is additionally important for assessment of mediastinal lymphadenopathy readily missed on plain films (Rostock 1983). Abdominal–pelvic CT allows for the preoperative identification of suspicious nodal areas, helps in the determination of radiotherapy treatment ports, and provides a baseline for comparative assessment of response to treatment.[107] Increasingly, PET or MRI appears to

be more accurate than CT in determining HL involvement of bone marrow or extranodal sites.[118–122]

The treatment of HL varies according to stage, and risk groupings stratified by known prognostic markers, as determined by various clinical research consortia. Chemotherapy with or without radiotherapy may be used for patients with stage IA or IIA disease.[103,104] Low-dose (15 to 25.5 Gy) radiotherapy combined with chemotherapy has been shown to be effective and to lessen growth impairment in treated children.[123] Management protocols are also different for children who have attained full growth versus those who are still growing, because the standard, high-dose, involved-field radiation therapy used for HL can lead to considerable long-term growth effects in children and young adolescents. A multi-institutional study has shown that children with stage IA or IIA disease who obtain a complete response following two cycles of multiagent chemotherapy (VAMP) may complete an additional two cycles and receive no radiation therapy with similar outcomes.[105] Low-dose radiotherapy combined with multiagent chemotherapy is recommended for children who have stage IB, IIB, or IIIA disease, who have bulky disease, or who have extranodal lesions.[103–105] Children of a similar age with stages IIIB, IVA, or IVB disease are treated with more intensive chemotherapy in combination with low-dose involved-nodal or involved-field irradiation.[3,124,125] Unlike adult disease, advanced-stage pediatric disease is routinely treated with radiotherapy to good effect.[124,126] Stem cell transplant with high-dose chemotherapy is an option in patients with relapsing HL.[127]

With current treatments, more than 90% of all patients with HL, regardless of stage, initially achieve complete remission.[105,124] Prolonged remission and cure are achieved in ~90% of patients with early stage I or II disease and in children with high-risk HL; an event-free survival of 94% and overall survival of 97% are achievable in rapid early responders with risk-adapted, multiagent chemotherapy and low-dose involved-field radiotherapy.[125] Partial or slow responders with high-risk HL may yet achieve an event-free survival of 80% to 90% and overall survival of 80% to 95%.[128]

The long-term survival of patients successfully cured of HL has created additional concerns. Radiation therapy during the formative years of

development has resulted in growth arrest in addition to hypothyroidism, sterility, and pulmonary fibrosis.[129–132] All HL survivors, particularly those treated with both chemotherapy and radiation, also have an increased future incidence of secondary malignancies, specifically of the thyroid gland, breast, lung, gastrointestinal tract, and hematologic system, including acute nonlymphoblastic leukemia and non-Hodgkin lymphoma.[114,133–136] Such complications can be minimized through precise and proper selection of initial HL therapy and potentially with volume reduction and proton therapy.[137–140] Studies are under way to determine which patients can be treated with reductions in radiation dose and field size as well as tailored chemotherapy without jeopardizing treatment and long-term survival.[128,132]

Non-Hodgkin Lymphoma

Pediatric NHL represents 7% of pediatric cancers among children younger than 20 years, with an annual incidence of 800 cases in the United States.[141] NHL is uncommon among children below age 3 years and more common among males than females. Congenital and acquired immunodeficiency conditions are associated with increased risk of NHL, with most cases in immunocompromised hosts associated with EBV. EBV-associated Burkitt lymphoma accounts for ~85% of the cases in endemic Africa, compared to only ~15% of the cases in North America or Europe.[141] Outside of equatorial Africa, pediatric head and neck lymphomas account for ~10% of pediatric lymphomas.[142]

Prognostic factors in pediatric NHL include the histologic subtype of NHL, stage, age, disease site, tumor burden, chromosomal anomalies, and treatment response. Current clinically relevant categorization of NHL typically considers three groups, in line with the World Health Organization classification: mature B-cell NHL, ~55% (including Burkitt, Burkitt-like lymphoma/leukemia, and diffuse large B-cell lymphoma); lymphoblastic lymphoma, ~25% (including precursor T-cell and precursor B-cell lymphoma); and anaplastic large cell lymphoma, ~15% (mature T-cell and null-cell lymphoma).[141,143]

NHL in the pediatric population is staged with CT scan and/or MRI, plus radionucleotide bone scans for suspected bone disease. PET can identify abnormalities not seen on CT and is routinely done at many institutions in

lieu of gallium scans, although the definitive implication of whether changes on PET in staging and posttherapy should guide management remains debated. Given the potential for false-positive and false-negative results, in the case of residual lesions on imaging, therapeutic decisions should be based on biopsy confirmation or corroborating FDG PET imaging, depending on the protocol.

The most widely used staging system for pediatric NHL is the St. Jude Children's Research Hospital staging,[144] outlined in **Table 24.9**.

Table 24.9 St. Jude Staging Classification for Pediatric Non-Hodgkin Lymphoma

Stage	Characteristic
I	■ A single tumor (extranodal) or single anatomical area (nodal), excluding the mediastinum or abdomen
II	■ A single tumor (extranodal) with regional node involvement ■ Two or more tumors or nodal areas on the same side of the diaphragm ■ A primary gastrointestinal tract tumor, completely resected with or without involvement of associated regional nodes
III	■ Tumors (extranodal) or nodal areas on opposite sides of the diaphragm ■ All primary intrathoracic tumors (mediastinal, pleural, thymic) ■ All extensive primary intra-abdominal disease, unresectable ■ All paraspinal or epidural tumors
IV	■ Any CNS and/or bone marrow involvement

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Burkitt and Burkitt-like lymphoma/leukemia are classically recognized for rapidly evolving and aggressive clinical presentations, commonly involving the abdomen and nonjaw head and neck region for sporadic cases and typical jaw involvement for EBV-associated endemic cases.

Rapid diagnosis and immediate initiation of therapy are critical for these fast-growing cancers, because metabolic complications pose significant risk during the first week of treatment and any delays can be fatal. A number of effective treatment regimens have been described, consisting of short, pulsed therapies, including cyclophosphamide-based regimens over 4 to 8 months, for instance, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with triple-drug intrathecal therapy.[141,145] Head and neck presentations of B-cell NHL are associated with increased likelihood of central nervous system (CNS) involvement—a recognized adverse prognostic factor—as well as with less advanced disease or smaller tumors than those with other primary sites.[146] Using intensive therapy, as in the French Society of Paediatric Oncology LMB89 trial, outcomes for children presenting with head and neck B-cell NHL can be excellent and similar to patients presenting with primary sites outside the head and neck; 95.5% 4-year event-free and overall survival were reported in the LMB89 subcohort of 112 patients with B-cell NHL, 26% of whom had CNS involvement at diagnosis.[146]

Most pediatric patients with lymphoblastic lymphoma present with an anterior mediastinal mass, which may cause superior vena cava syndrome and manifest as swelling of the head and neck with or without evident respiratory distress. Typically, treatment regimens have been adopted from those for pediatric acute lymphoblastic leukemia, with multiagent chemotherapy regimens for 18 to 30 months.[147] With this strategy, the Berlin-Frankfurt-Munster (BFM) group reported 5-year disease-free survival of up to 90%.[141,143]

Tumor lysis syndrome is an oncologic emergency that is particularly common in children with NHL, due to rapid cellular proliferation and turnover. Tumor lysis syndrome may occur spontaneously or upon initiation of therapy. The resultant metabolic derangements (hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia) and associated sequelae can be acutely life threatening, warranting anticipatory and vigilant

management.[148]

Large cell lymphomas can be heterogeneous in biology and response to therapy, and various treatment approaches have been adopted over time, including shorter-term multiagent therapies requiring hospitalization for fewer than 6 months, and year-long regimens that may be administered on an outpatient basis, such as those based on the APO backbone (doxorubicin, prednisone, vincristine).[141,147,149] Event-free survival rates approximate 70%.[145]

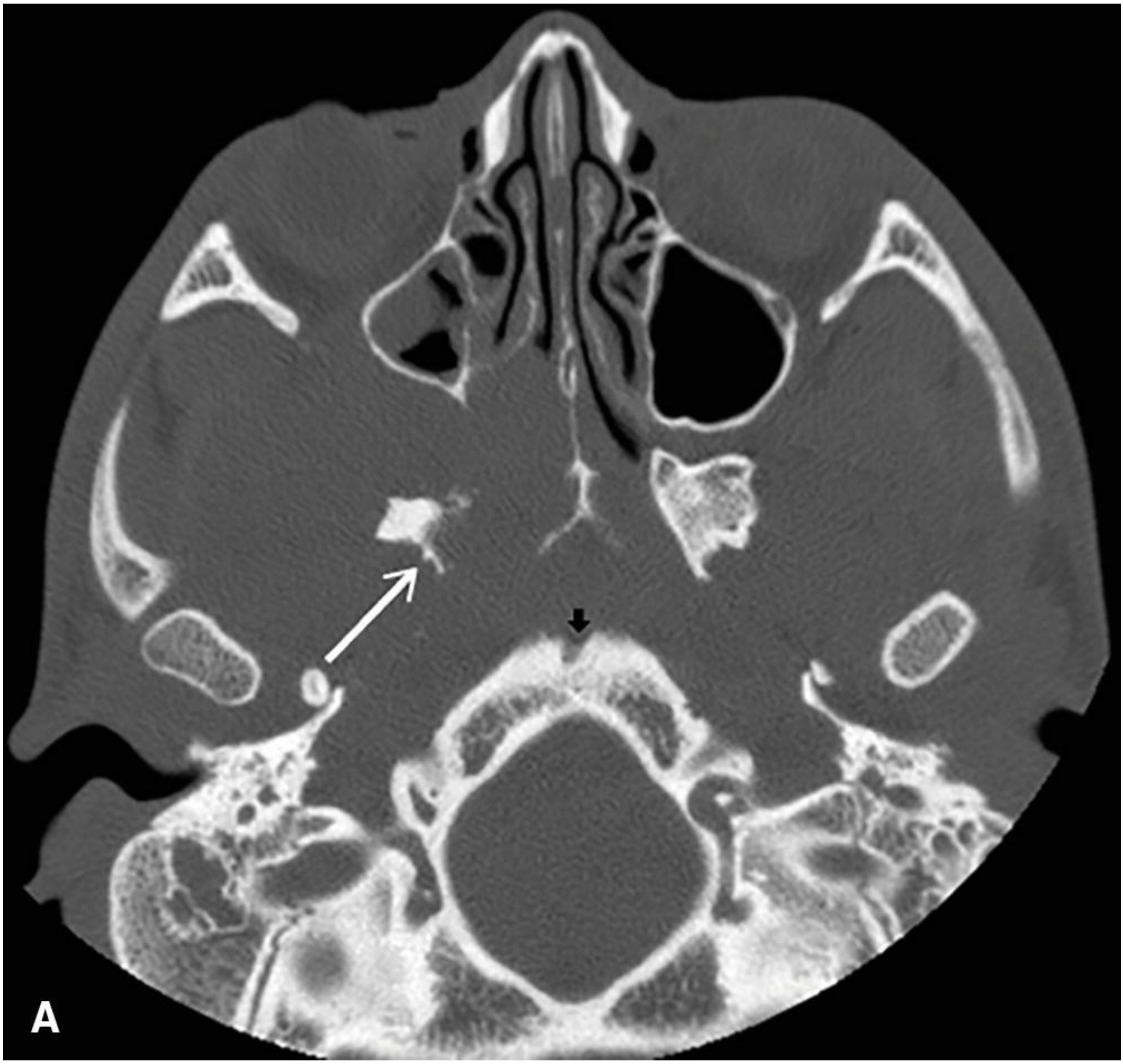
Radiation therapy is rarely needed in children with NHL, given excellent outcomes with chemotherapy and intrathecal therapy for CNS control.[141] Over time, prophylactic CNS radiation has been safely omitted for lymphoblastic lymphoma without increased CNS relapse, allowing CNS radiation to be reserved for children presenting with CNS disease.[150] Therapeutic CNS radiation has also been safely omitted for patients with B-cell NHL and anaplastic large cell lymphoma, even in the presence of CNS disease. Appropriate staging and judicious use of intrathecal chemotherapy remain keys to attaining successful oncologic outcomes with minimization of morbidity.[141]

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) contributes to ~30% of cancers involving the upper airway, with an annual incidence of ~0.8 per million children below age 15 years and 1.3 per million children between 15 to 19 years of age in North America.[151] Racial and geographic variability has been demonstrated, including increased incidence in Southeast Asia, North Africa, and the Mediterranean region and among males and black young people.[151–153] Of the three WHO histologic subtypes of NPC, type III undifferentiated carcinoma is the most commonly seen in children.[151,153,154] Among other distinctions from adult NPC patients, an analysis of SEER data found that children and adolescents below age 20 years more often exhibited advanced NPC disease, yet had improved 5-year survival of 83% compared to 62% in adults.[153]

NPC is well associated with EBV; in some settings, EBV serology as well as circulating EBV DNA levels have been used to support early diagnosis and disease prognostication.[151,155]

Common clinical presentation for pediatric NPC includes cervical adenopathy, often bilateral in nature, along with hearing loss, epistaxis or nasal obstruction, and headache.[154,156] MRI of the head and neck, with and without contrast, is recommended and should include sequences to assess cervical and supraclavicular lymphadenopathy for accurate staging (**Fig. 24.9**). CT scan may help detect destructive changes involving the skull base although MRI is preferred for determining the extent of intracranial tumor extension and skull base involvement.[157] Baseline and follow-up dental x-ray (panorex) with dedicated otolaryngology and dental evaluations are also warranted. Metastatic workup should be done, typically including a CT chest (with contrast, to include evaluation of lymphadenopathy) and a bone scan.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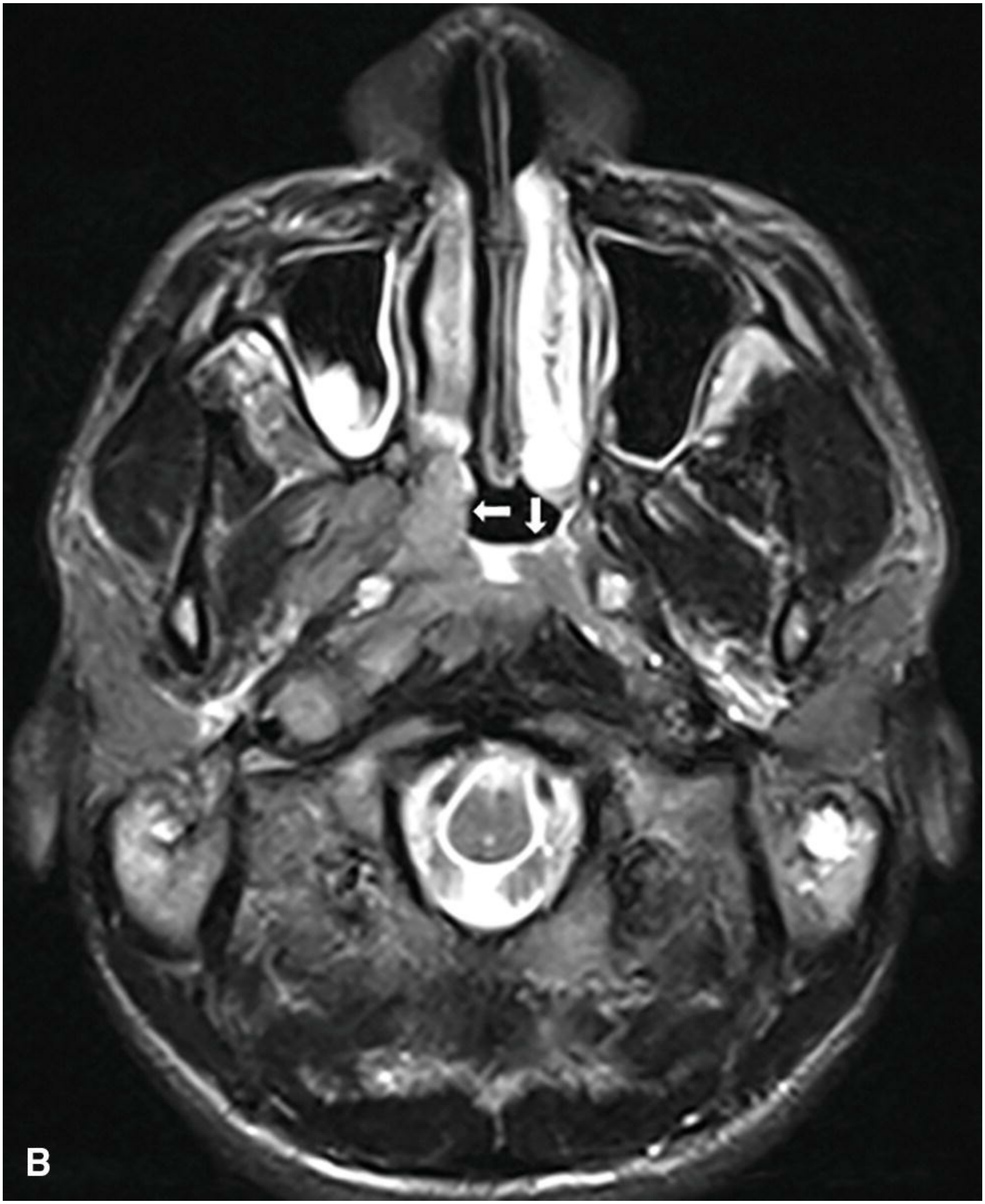
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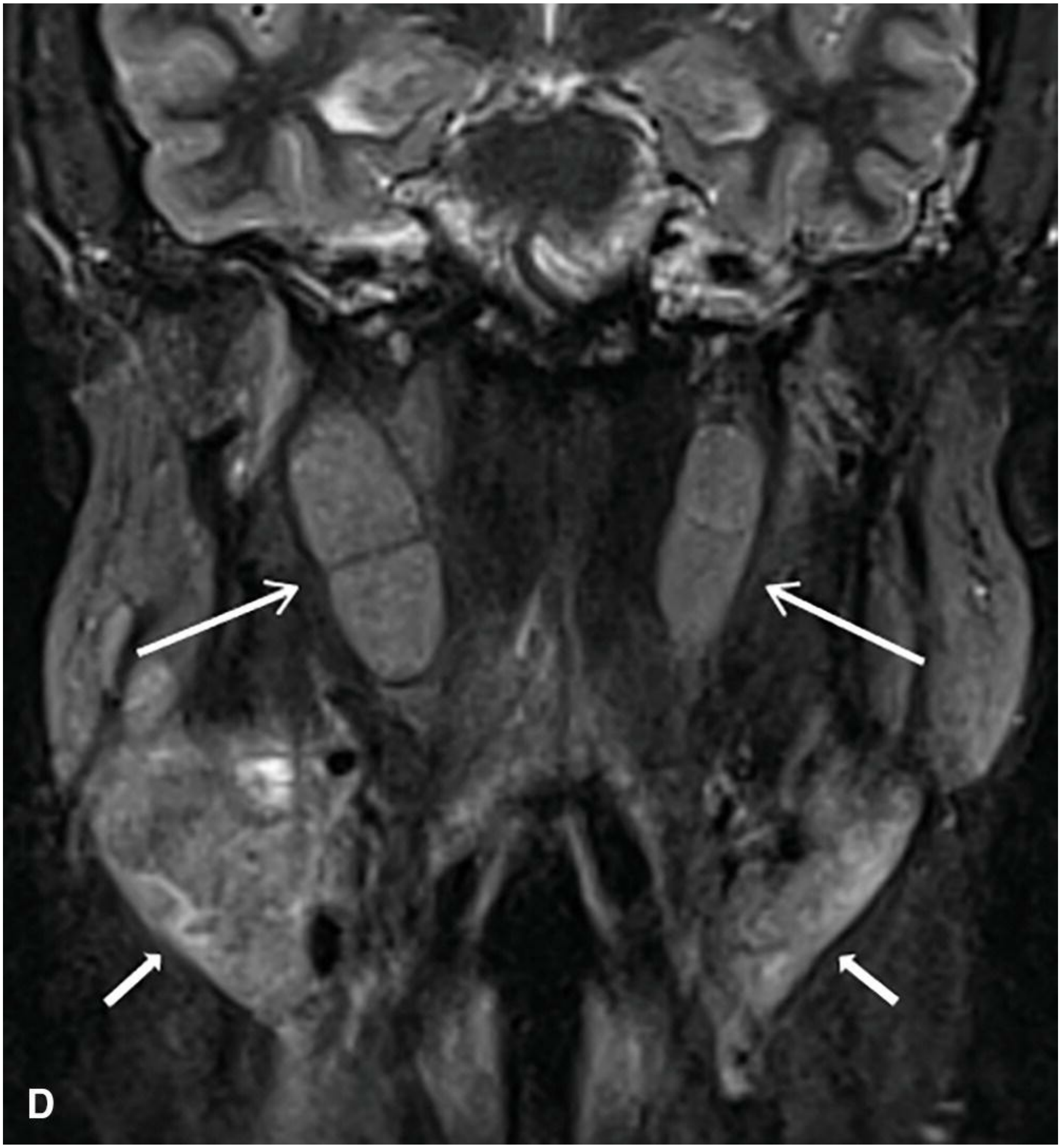


Figure 24.9. A: An axial CT scan image of the skull base of an 18-year-old patient with biopsy-proven NPC shows destruction and sclerosis of the right pterygoid process (*white arrow*) and erosion of the clivus (*small black arrow*). **B:** An axial T2-weighted image through the skull base demonstrates prominent soft tissue in the nasopharynx (*arrows*), more prominent on the right than on the left. **C:** A postgadolinium axial T1-weighted image reveal enhancing tumor expanding and extending from the right pterygopalatine fossa (*small arrow*) into adjacent skull base structures (*large arrow*). **D:** A

coronal STIR image shows markedly enlarged retropharyngeal lymph nodes (*large arrows*) and prominent bilateral lymph nodes at level II of the neck bilaterally (*small arrows*).

FDG PET-CT may also be helpful in the staging and follow-up of pediatric NPC patients; although potentially underestimating tumor extent and adenopathy compared to MRI at baseline, it can help to delineate nonspecific findings and metastatic disease and may reflect earlier disease clearance on therapy than on MRI.[158] Baseline audiogram should be performed. Stage is described as in adults, according to the American Joint Committee on Cancer.[151]

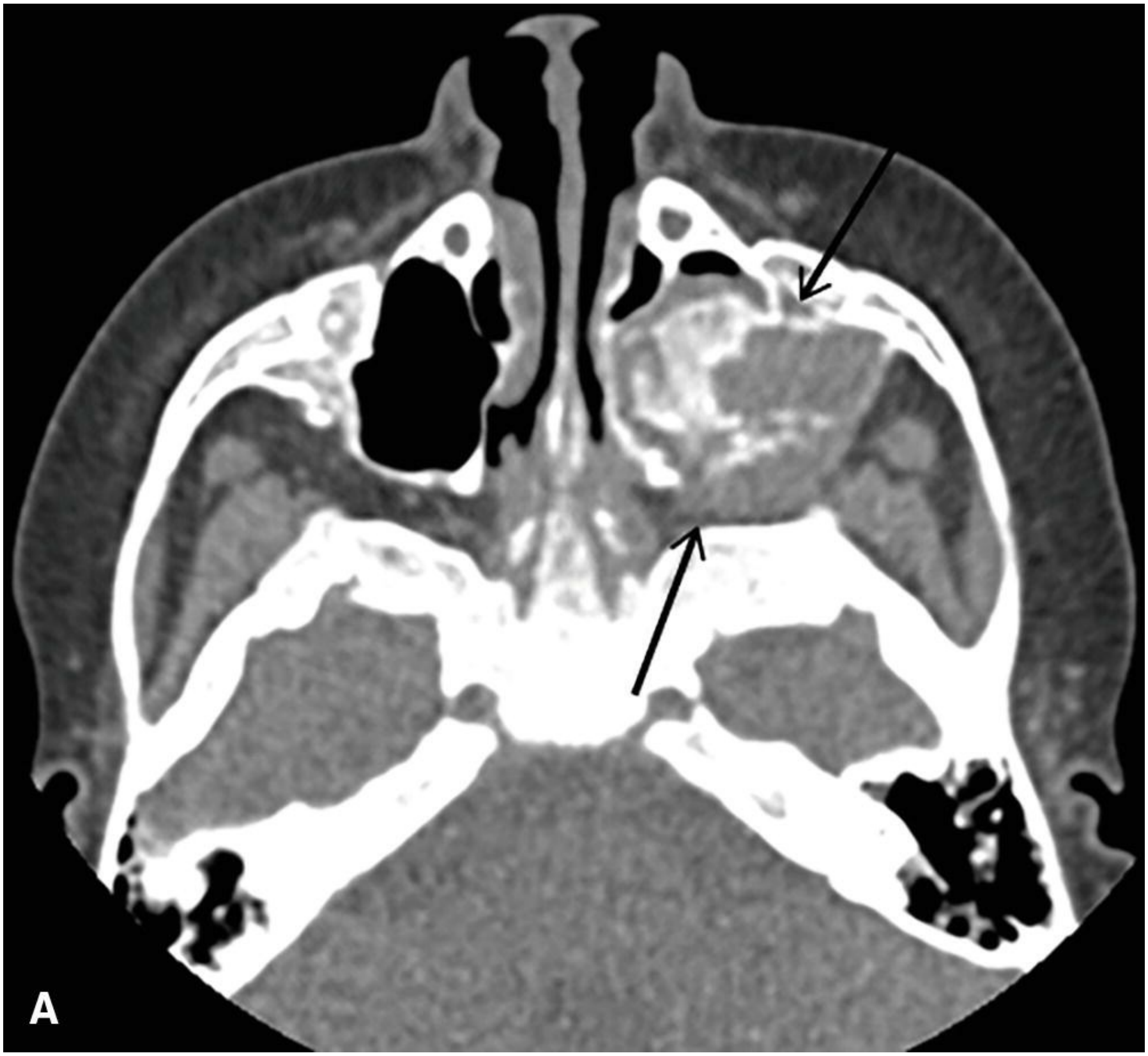
Multimodality therapy, including cisplatin-based chemotherapy and targeted radiotherapy, has optimized the survival of children with NPC in recent decades, with overall and event-free survival approximating 80% and higher.[159,160] The backbone of current international pediatric NPC therapy for most children who present with advanced disease involves cisplatin-based induction chemotherapy, followed by concomitant radiation (dose tailored to stage and/or response) and cisplatin chemotherapy.[159,160] The location and local spread of NPC renders it an unlikely candidate for extensive surgery, such that surgery is typically limited to diagnostic biopsy, often with involved accessible lymph nodes.[151] Treatment-related complications among survivors warrant ongoing evaluation.[154,159] An institutional retrospective review of 59 pediatric patients from 1961 to 2004 found 15-year event-free survival rates of 64%, with improved survival (to 75%) after 1980. However, in this cohort where all received primary tumor radiation, and 98% received cervical radiation therapy and 88% received chemotherapy, the analysis also identified the 15-year cumulative incidence of significant morbidity to be 84%, including estimated specific cumulative incidences of 53% for sensorineural hearing loss, 43% for primary hypothyroidism, and 14% for growth hormone deficiency.[154] In this group, 8.5% of (n = 5) patients developed secondary malignancy, consistent with other analyses suggesting increased risk of second malignancy in pediatric NPC survivors than adult patients.[153] With the interest to ameliorate acute and late toxicities while maintaining optimal outcomes, a response-based radiotherapy treatment approach has been proposed. Orbach et al.[161] retrospectively analyzed outcomes in 34 children with advanced NPC over nearly three decades. They

found that approximately half of these children could be treated with reduced doses below 50 Gy to the involved neck when a good clinicoradiologic response from neoadjuvant chemotherapy was obtained, without compromising outcomes compared with others receiving a median of 60 Gy. The authors concluded that a response-based treatment paradigm is feasible.[161] This, in part, aided the rationale for the latest Children's Oncology Group study, ARAR0331, which, at the time of writing, has been closed to accrual with reported outcomes pending.

In the setting of refractory or relapsed NPC, emerging therapies under investigation have included EBV-specific cytotoxic T lymphocytes, with potential sustained benefit for those with locoregional disease.[162,163] Surgery can have a role in the treatment of patients with limited local or regional recurrences.

Neuroblastoma

Neuroblastoma represents the most common extracranial solid tumor seen in childhood. It is a tumor of the neural crest cells in the sympathetic nervous system, and 90% of cases are diagnosed in patients below 5 years of age. More commonly a metastatic lesion than a primary tumor of the head and neck, metastatic neuroblastoma to the head and neck may take various forms[164] (**Fig. 24.10**). Proptosis and periorbital ecchymosis (classically described as "raccoon eyes") may be seen in patients with retrobulbar metastatic disease. Stellate ganglion involvement may lead to presentation with Horner syndrome. Subcutaneous skin nodules may be seen diffusely, including in the scalp, most often in infants. Infrequent cases of adolescents presenting with neuroblastoma may more likely involve less typical metastatic sites, including the brain. Paraneoplastic phenomena, including opsoclonus/myoclonus, may also be seen with neuroblastoma; although often associated with favorable biology tumors, neurologic sequelae may be persistent even after therapy.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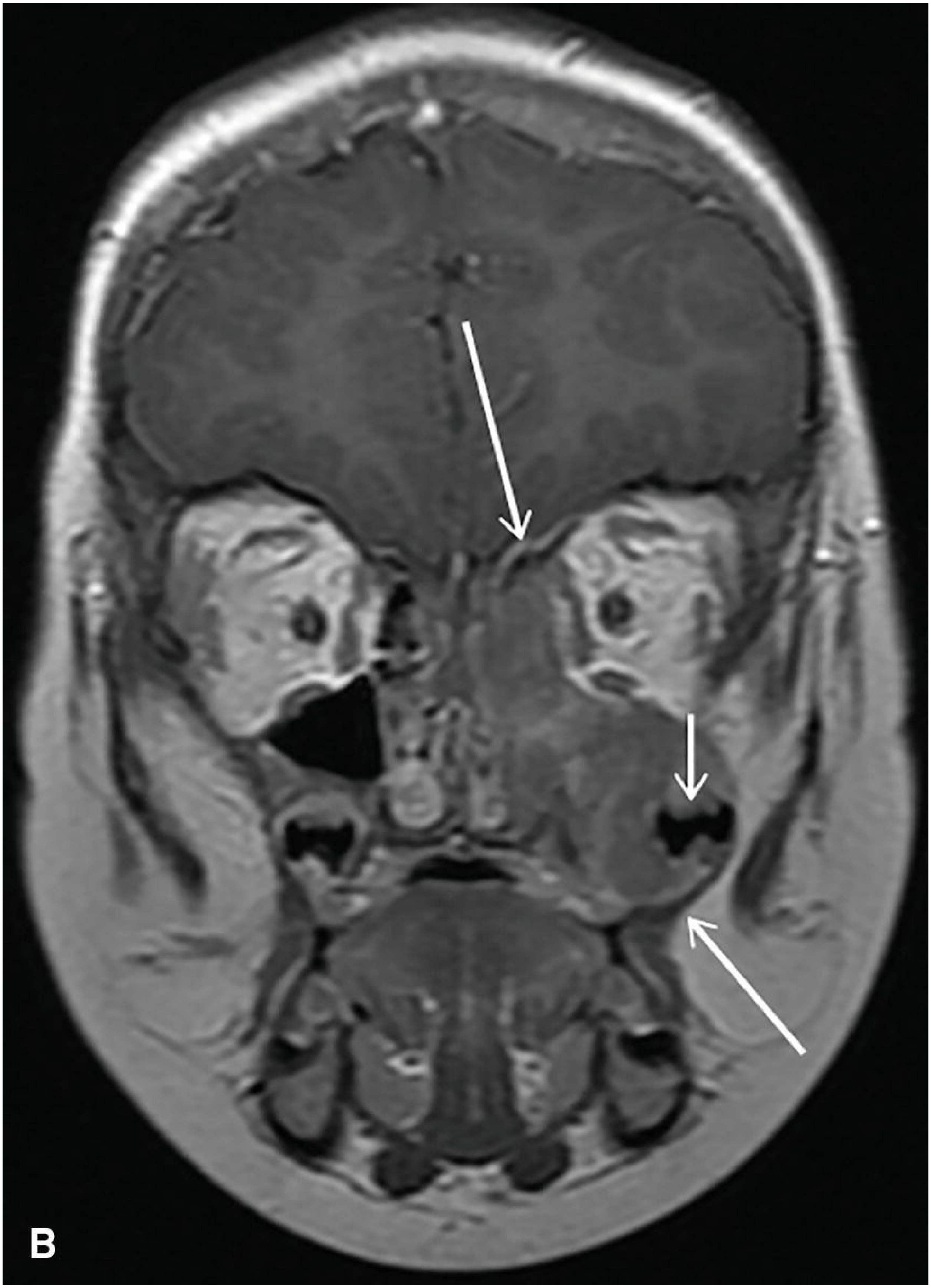
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Figure 24.10. A: An axial unenhanced CT scan image through the paranasal sinuses reveals a destructive mass (*arrows*) centered in the left maxillary sinus of a 2-year-old child that extends into the left pterygopalatine fossa. **B:** A postgadolinium coronal T1-weighted image shows the lesion (*arrows*) to also involve the ethmoid air cells on the left. A maxillary tooth (*small arrow*) is enveloped by the mass. Axial T2-weighted **(C)** and postgadolinium coronal T1-weighted **(D)** images demonstrate marked expansion of the skull base (*arrows*) with intracranial epidural extension of tumor. After biopsy, the mass was determined to be neuroblastoma, likely metastatic from an adrenal gland primary.

Primary cervical neuroblastoma is generally uncommon, representing fewer than 5% of all cases.[165] In a recent analysis of 8,369 patients in an international registry cohort, primary tumor site was the adrenal in 47%, abdomen/peritoneum in 24%, thorax in 15%, and pelvis in 3%, with only 3% in the neck and 8% in varied other sites.[166] As the largest multivariate analysis to date of neuroblastoma primary site on outcomes, it supported earlier smaller series that suggested patients with primary cervical neuroblastomas as typically having favorable biologic features such as absence of MYCN amplification and also as independently having more favorable overall outcomes even after controlling for age, stage, and MYCN amplification status. Notably, patients with cervical neuroblastoma remained at risk for local recurrence, likely related to its challenging location for complete resection.[166]

Isolated cases of primary neuroblastoma of the head and neck have also been reported in children in sites such as the maxillary sinus,[167] retropharynx, and parotid gland.[168]

International minimum criteria for definitive diagnosis of neuroblastoma involve either an unequivocal pathologic diagnosis from tumor tissue or a bone marrow involvement with tumor cells coupled with increased urinary catecholamine metabolites.[169] Measurement of urinary catecholamines, typically homovanillic acid (HVA) and vanillylmandelic acid (VMA), can be done via spot urine measurements in lieu of 24-hour urine collections. LDH and ferritin have also been used as key additional laboratory markers at baseline for potential prognostication. Bilateral bone marrow aspirate and biopsy are part of the typical staging. Tumor biology is vital to the

International Neuroblastoma Pathology Classification (INPC), with adequate tumor cells needed to determine key features including MYCN copy number, tumor cell ploidy (DNA index), and segmental chromosomal changes. Expert cellular classification is warranted to distinguish the spectrum of neuroblastic tumors that may be seen, from benign mature ganglioneuromas, less mature ganglioneuroblastoma, to malignant immature neuroblastoma, with very different implications for management. In addition to cross-sectional imaging using CT or MRI, metaiodobenzylguanidine (mIBG) scans are used in staging for neuroblastoma, with semiquantitative scoring methods developed to help gauge disease extent and guide prognostication.[170,171] For neonates and infants, ultrasound can be a helpful modality, including for follow-up.

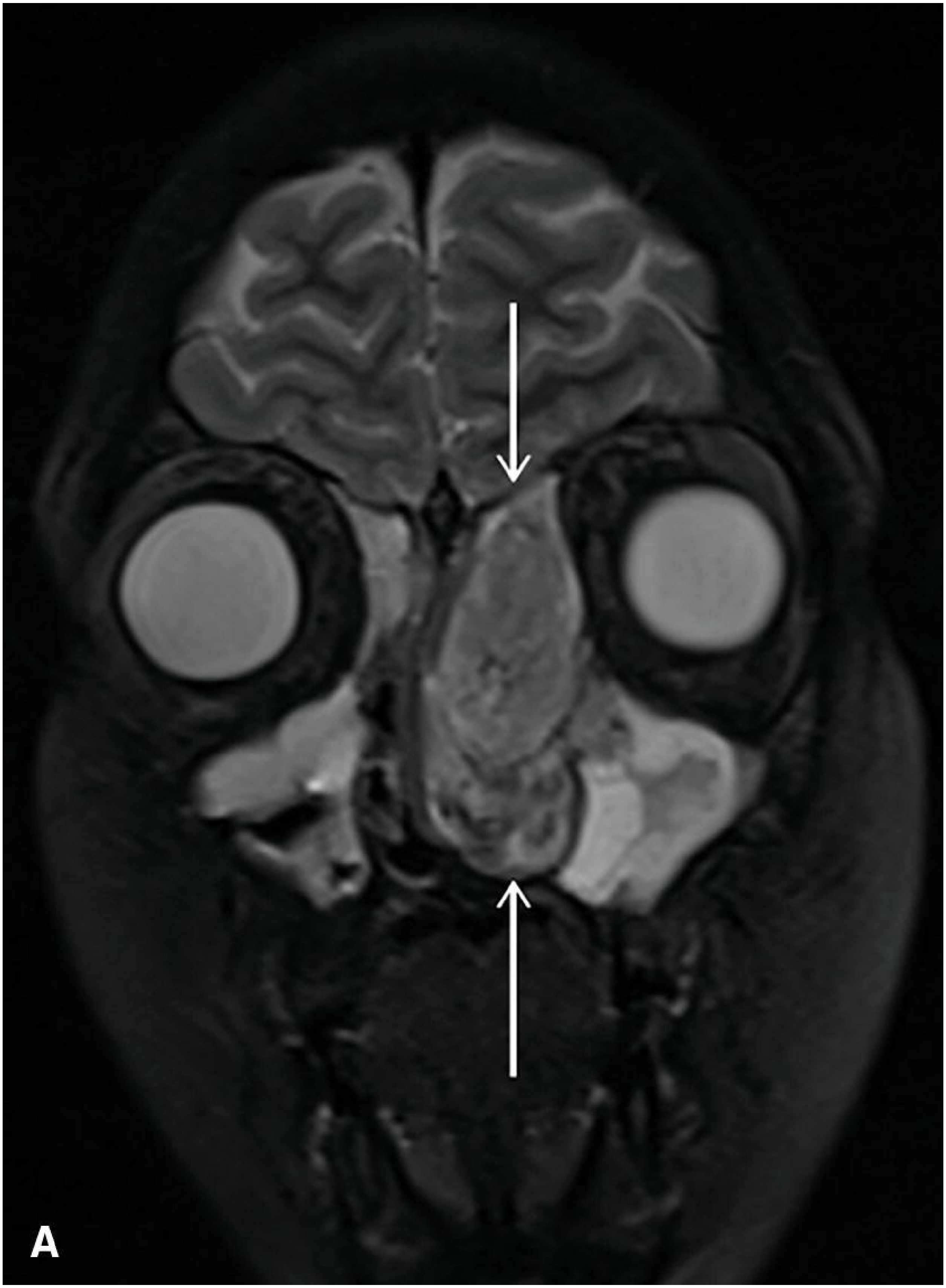
The International Neuroblastoma Staging System (INSS) is a postoperative staging system widely in use for more than two decades to help guide risk group stratification and treatment.[169] With evolving understanding, and to allow preoperative staging and minimize staging inconsistencies due to local surgical access and practices globally, the International Neuroblastoma Risk Group (INRG) staging system was developed, incorporating the presence of image-defined risk factors and metastases prior to surgery or therapy.[172] Staging is incorporated with patient age, pathology classification, and tumor biology into generally three risk categories: low risk (characterized by observation or surgical resection alone), intermediate risk (chemotherapy typically prior to surgical resection; overall well tolerated with excellent overall survival above 95%),[173] and high risk (intensive multimodality therapy including hematopoietic stem cell transplantation, radiation therapy, differentiation therapy, and immunotherapy, with survival rates still typically only ~40%).[174]

Infants constitute a special group of patients with neuroblastoma, in which small asymptomatic localized neuroblastoma tumors may be electively observed with appropriate monitoring and supportive care, with many altogether avoiding all surgery including biopsy[175] and many spontaneously regressing, with initial regression one to 18 months after diagnosis.[176] However, infants below three months of age who have progressive symptomatic neuroblastoma, including abdominal distension with hepatomegaly or cardiorespiratory compromise risk, typically warrant chemotherapy for symptom control. Infants aged 12 to 18 months and below thus constitute a special group, with typically very favorable prognosis even

in the setting of metastatic disease limited to skin, liver, and <10% of the bone marrow, constituting a special stage, 4S (for infants below age 12 months with localized primary tumor) in the INSS classification and MS (expanded to infants below 18 months and regardless of primary tumor extent) in the recent INRG classification. This typically more favorable prognosis for infants also extends to those with advanced metastatic disease (stage 4) without unfavorable MYCN amplification.[173,177] Given the significant biologic and clinical heterogeneity of neuroblastomas, multidisciplinary management by specialized teams is critical.

Esthesioneuroblastoma

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a tumor arising from the nasal neuroepithelium, distinct from conventional neuroblastoma. It is a rare malignancy in children with fewer than 100 children described to date; most cases develop after age 10 years, commonly with advanced disease.[151,178,179] Presentation is varied, including exophthalmos and nasal obstruction or, in rare instances, hyponatremia.[151,180] Along with CT and MRI, PET-CT may be beneficial in disease staging[151,178] (**Fig. 24.11**). As in adults, the Kadish clinical staging system (stages A to D) is most widely applied. Surgery and radiation therapy have traditionally played dominant roles, with chemotherapy also demonstrating effect in small series of children with advanced disease.[178,181] Favorable 5-year survival rates of 80% to 90% have been described.[178,181]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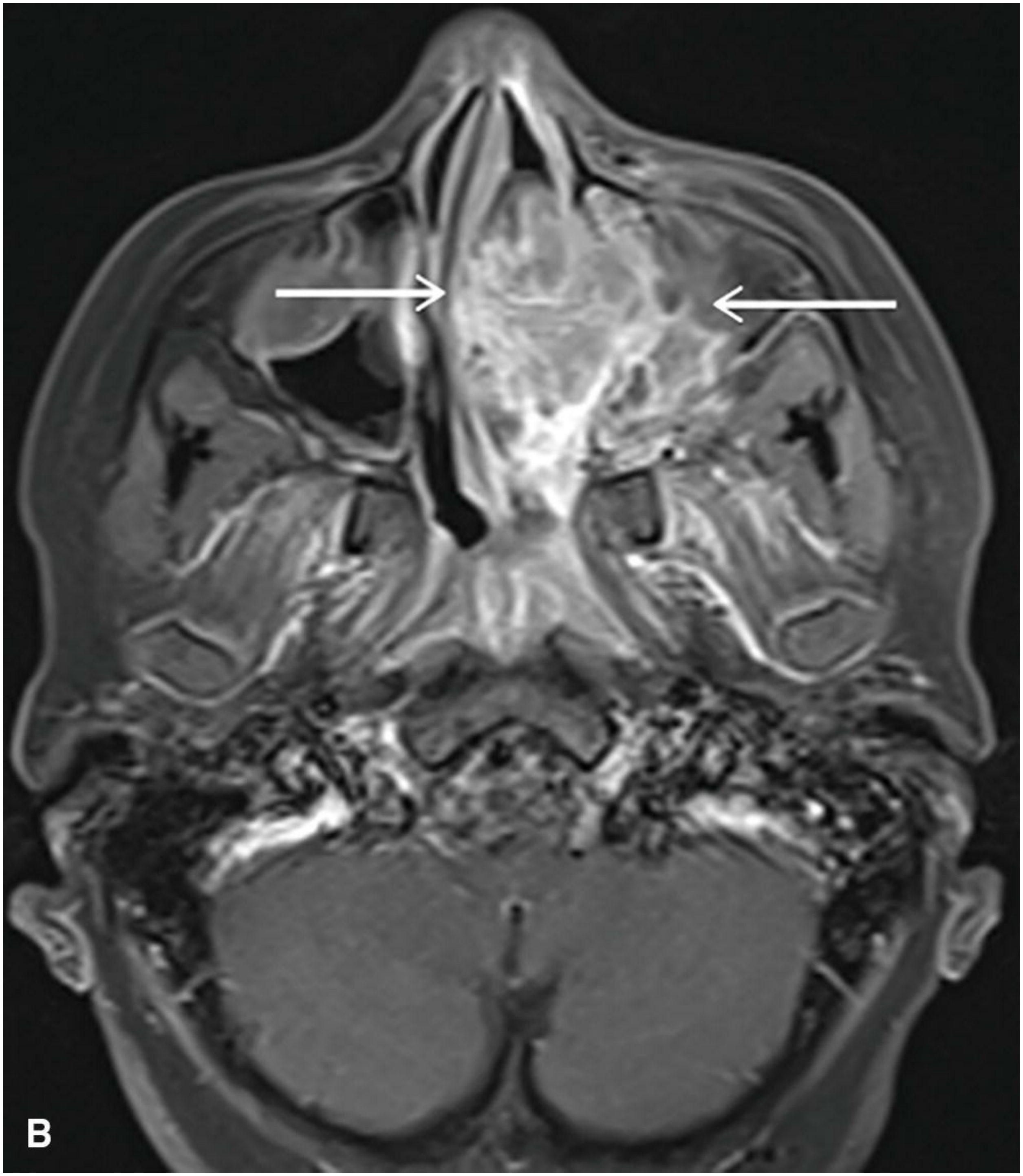
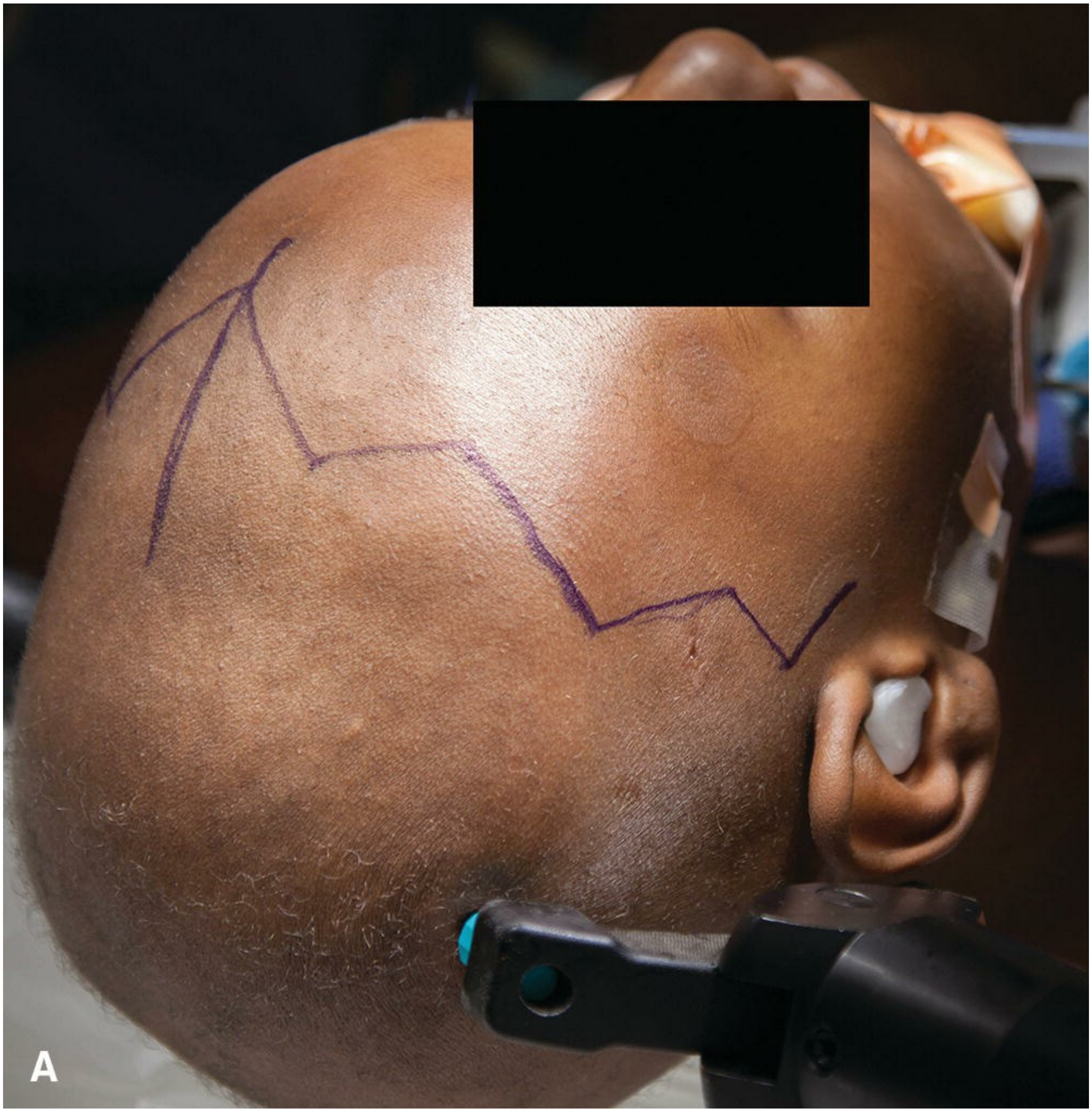


Figure 24.11. Fat-saturated coronal T2-weighted **(A)** and fat-saturated postgadolinium axial T1-weighted **(B)** images of the face for a 14-year-old patient show a large mass (*arrows*) with heterogeneous signal intensity and heterogeneous enhancement in the left nasoethmoidal region with extension into the left maxillary and frontal sinuses. Biopsy demonstrated the lesion to be an esthesioneuroblastoma.

Retinoblastoma

Retinoblastoma arises in the retina and represents the most common intraocular cancer in the pediatric population. Approximately 9,000 new cases of retinoblastoma are expected globally each year,[182] and almost all occur in patients under 5 years of age. Patients with bilateral retinoblastoma present particularly early, most often within the first year of life. Leukocoria is the most common presenting feature symptom in most settings[182]; tumors that have progressed may present with painful buphthalmos, as well as orbital and distant metastatic disease involving the bone marrow and bones. Appropriate examination under anesthesia is critical to guide diagnosis and ongoing management of retinoblastoma. MRI is typically preferred in delineating tumor extent.[183] For suspected advanced disease, additional metastatic workup is typically performed, including bilateral bone marrow aspirates and biopsies, lumbar puncture, and bone scans (**Fig. 24.12**).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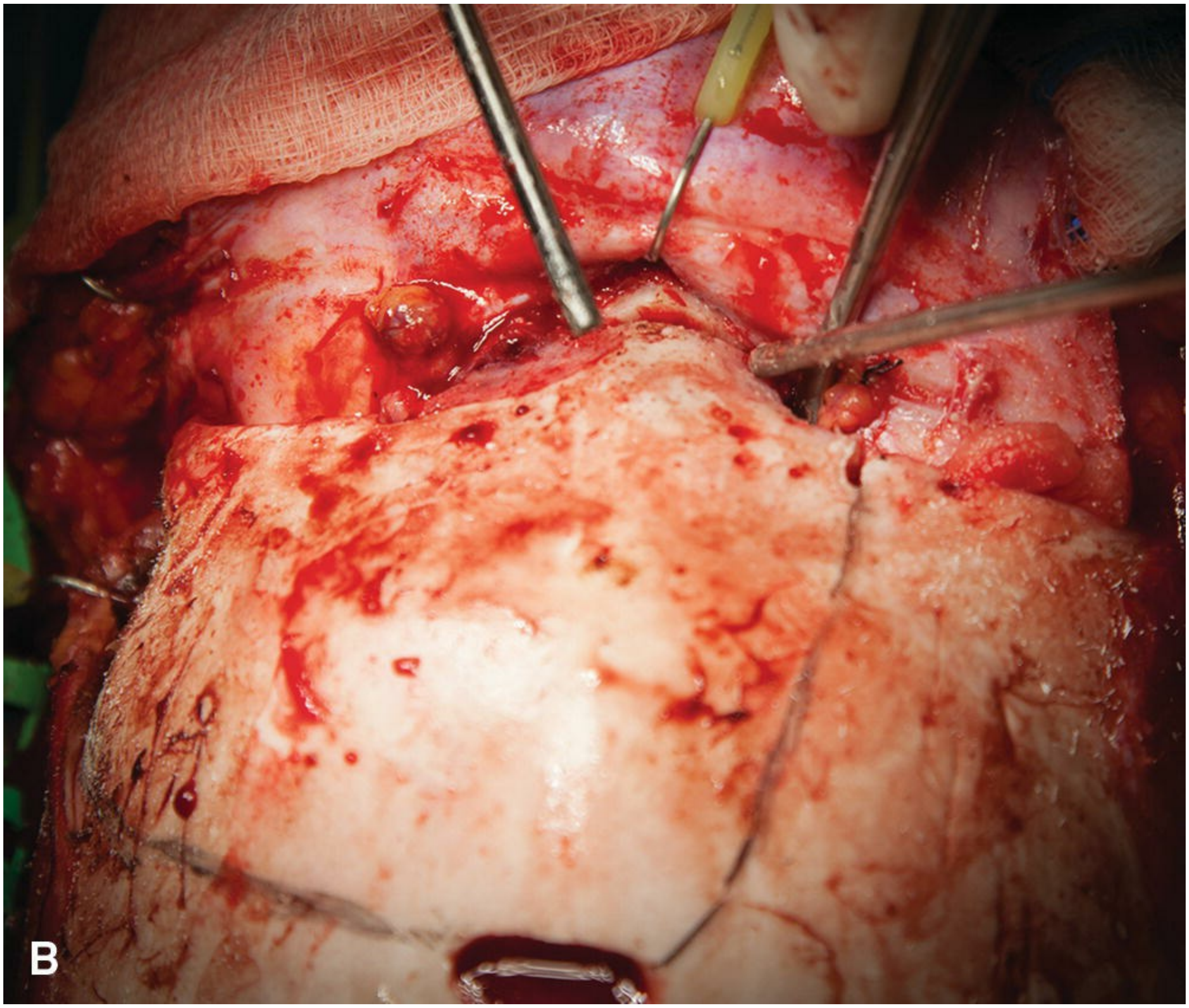
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Figure 24.12. A: Bicoronal subcranial approach for myxoid chondrosarcoma arising from the frontoethmoid complex. **B:** Excision of tumor via subcranial approach. **C:** Tumor involving the frontal bone.

Approximately 30% of retinoblastoma is heritable, most often characterized by a germline mutation in the RB1 gene (on chromosome 13), of which 75% may be de novo. All children with bilateral retinoblastoma and an estimated 15% of those with unilateral retinoblastoma are expected to have heritable retinoblastoma. Genetic evaluation and counseling constitute an important part of management, as those with germline mutation are at increased risk for developing subsequent tumors, including in the opposite

eye, or as trilateral retinoblastoma, with development of an intracranial malignant tumor, classically involving the pineal gland. They are also at increased risk for subsequent neoplasms that may manifest in adulthood.[182] Emerging genetic insights have also expanded the appreciation of retinoblastoma genetic complexity, with cases that can present at an early age without RB1 inactivation, demonstrating tumor cell–specific MYCN amplification.[184,185]

With modern multidisciplinary management in North America and other developed regions of the world, retinoblastoma has progressed in the last century from a disease associated with almost uniform mortality to one with >95% survival, with progressive treatment focused to allow more than 90% of patients to retain their eyes as well as visual function.[186] Due to the very young age and developmental vulnerability of most patients with retinoblastoma, tailored management and consideration of late effects such as hearing loss from ototoxic chemotherapy, as well as second malignancies, are particularly important.[186,187]

Salivary Gland Tumors

Tumors arising in the salivary glands in children are uncommon. In a review of 80 patients seen over a 58-year period at Children's Hospital in Boston, 25 were found to have epithelial tumors, whereas 55 had nonepithelial tumors. Among the epithelial tumors, 10 were pleomorphic adenomas, whereas the rest were malignant tumors with mucoepidermoid carcinoma being the common pathology. Capillary hemangioma was the most common nonepithelial tumor with a distinct predilection for females.[188]

Less than 5% of all salivary gland carcinomas affect children under the age of 19 years with an annual incidence of 0.8 per million.[189] Salivary gland tumors are more often malignant in the pediatric age group than in adults. Mucoepidermoid carcinoma is the most common tumor followed by acinic cell carcinoma. The parotid gland is the most common site of origin. Adenoid cystic carcinoma, adenocarcinoma, and squamous cell carcinoma occur very rarely in children. Compared to adults, pediatric salivary gland carcinomas are more often localized and of lower histologic grade.[189,190]

Most children with salivary tumors present with a painless mass in the region of the parotid gland. CT is the most commonly employed investigation

to help establish the extent of disease, spread to neighboring tissues, and presence of metastatic lymphadenopathy. MRI may be indicated to evaluate the extent of spread beyond the confines of the parotid into the skull base and along cranial nerve foramina, if such spread is suspected. Chest imaging is indicated for malignant lesions to rule out metastatic spread. Fine needle aspiration cytology is helpful in establishing a pathologic diagnosis, but rates of accuracy in the pediatric population are not well established. An open incisional biopsy is generally discouraged but may be considered in rare selected cases provided it is performed by an experienced head and neck surgeon.

Surgical excision of the involved gland is the mainstay of treatment. A superficial or total parotidectomy with preservation of the facial nerve and its branches must be performed. If the nerve or one of its major branches has to be sacrificed due to encasement by tumor, immediate interposition grafting should be performed along with static facial reanimation as indicated. Excision of the submandibular gland is necessary for tumors arising in this location. A modified radical neck dissection is indicated if there is metastatic lymphadenopathy present. Elective neck dissection in the absence of lymphatic metastasis is not indicated except in cases of high-grade malignancy. Postoperative radiation therapy may be withheld if surgical margins are negative and the tumor is low or intermediate grade. High-grade histology, adenoid cystic carcinoma, perineural or lymphovascular invasion, and presence of metastatic lymphadenopathy warrant postoperative radiation treatment.

Chemotherapy is generally limited to the treatment of metastatic or inoperable recurrent cancers. Cisplatin or carboplatin, paclitaxel, and gemcitabine among other agents have been used singly or in combination with only modest responses and no discernible effect upon survival. There is also considerable interest in therapies directed toward specific molecular targets such as c kit, EGFR, and HER2, but the results thus far have not met expectations. Recently, there has been an interest in cisplatin-based concurrent chemoradiation in the adjuvant setting for high-risk salivary gland cancers. A phase II randomized Radiation Therapy Oncology Group Trial (RTOG 1008) comparing postoperative radiation to chemoradiation in this setting is currently ongoing. However, individuals younger than 18 years of age are not eligible for the study.[191]

For salivary gland carcinomas in the SEER database diagnosed between 1973 and 2006, prognosis was significantly better in the pediatric age group compared to adults (5-year overall survival 95% compared with 59%, $p < 0.001$).[189] Predominance of tumors of a lower histologic grade and more limited extent is thought to have contributed to this more favorable outcome.

Thyroid Carcinoma

Cancer of the thyroid gland is uncommon in children. An analysis of the April 2008 release of SEER data revealed a total of 1,753 cases of thyroid carcinoma diagnosed from 1973 to 2004 in patients younger than 19 years of age. The age-adjusted population incidence was 0.89 cases per 100,000 females and 0.2 cases per 100,000 males. The incidence was highest in the 15 to 19 years age group at 1.6 per 100,000 patients. Tumors were classified as papillary in 60% of the cases, whereas follicular variant of papillary, follicular, and medullary cancers made up 23%, 10%, and 5% of cases, respectively.[192]

The incidence of thyroid cancer in children appears to be rising. Data from the National Program of Cancer Registries and SEER for the years 2001–2009 showed an increasing trend with an annual percentage change of 4.9%.[193] This is in keeping with an increase in incidence noted in adults. The cause is unclear. Exposure to radiation by CT or dental radiographs as well as to chemicals such as perchlorate and polybrominated diphenyl ethers has been proposed, but definitive evidence is lacking. It is also possible that the trend is related to improved diagnosis.

Exposure to radiation increases the risk of thyroid cancer. Dramatic increase in the incidence of thyroid cancer has been noted after the atomic blasts in Japan as well as the Chernobyl disaster in 1986.[194] The latency period between radiation exposure and onset of cancer is typically 10 to 20 years, but thyroid cancer has been seen as early as 5 years after exposure in some children.[195] Thyroid cancer is the most common second malignancy in children treated for Hodgkin and non-Hodgkin lymphoma.[195] Hence, screening with thyroid ultrasound is warranted in individuals with a history of prior radiation exposure starting 5 years after the exposure.

Although most cases of nonmedullary or differentiated thyroid cancer are sporadic, clustering within families has been noted occasionally. Familial

nonmedullary thyroid cancer displays features of clinical “anticipation” with the second generation acquiring the disease at an earlier age and having more advanced disease at presentation.[196] Many rare genetic syndromes such as Cowden syndrome, Gardner syndrome, and Werner syndrome are also associated with an increased incidence of thyroid carcinoma. Additionally, mutations in RET proto-oncogene can cause medullary thyroid carcinoma either as part of multiple endocrine neoplasia, types 2A and 2B, or as familial medullary thyroid carcinoma.

RET/PTC gene rearrangements are common in children with papillary thyroid carcinoma. Although BRAF mutations are seen in as many as 45% of adults with papillary thyroid carcinoma, these mutations are less common in children.[195,197]

A nodule in the thyroid gland is the most common clinical presentation in children with differentiated thyroid carcinoma although occasionally a mass in the lateral neck due to lymphatic metastasis may be the first presenting symptom. A thyroid nodule in the pediatric age group is significantly more likely to harbor malignancy when compared to adults. Although the incidence of malignancy varies widely in the literature, in one study with standardized assessment in a series of 300 consecutive children with thyroid nodules, 22% were found to have cancer compared to 14% in a control population of adults with thyroid nodules from the same center.[198] Children with thyroid carcinoma are much more likely to present with lymph node metastasis compared to adults. Also, distant metastasis is noted in 20% to 30% of children at presentation.[195]

A TSH level must be obtained when assessing a thyroid nodule to rule out a hyperfunctioning nodule. The vast majority will have normal thyroid function and will require a thyroid ultrasound as the next step in diagnostic workup. All nodules that are 1 cm or greater in size must be evaluated with a fine needle aspiration biopsy. Even smaller nodules may need aspiration if there are microcalcifications or abnormal perithyroidal lymph nodes seen on ultrasound. History of thyroid cancer in the family or one of the aforementioned tumor syndromes or prior radiation exposure should also prompt needle aspiration for nodules smaller than 1 cm. Most children tolerate this procedure well. Malignant nodules are more likely to be solid in nature and larger in size. The presence of calcification and abnormal lymph nodes in the central compartment or in the lateral neck also predicts for

malignancy but has limited sensitivity due to low incidence of these features. The Bethesda System for Reporting Thyroid Cytopathology is commonly utilized for classifying the nodules. Patients with benign cytology can be safely followed unless the nodule is >4 cm in size as the predictive accuracy of a benign result in this group has been shown to be lower.[198] Those with malignant cytopathology will typically require a near total thyroidectomy. A diagnostic lobectomy is generally recommended in patients with indeterminate cytology. Although molecular profiling tests have recently been used with acceptable accuracy in adults to predict malignancy in nodules with indeterminate cytology, their use in the pediatric population has not been adequately studied.

More detailed anatomic imaging with MRI may be indicated in children presenting with symptoms and signs of airway invasion or compression for the purpose of preoperative planning.

Due to higher rates of lymphatic and distant metastasis at presentation, and a higher rate of recurrence in children with thyroid cancer, the threshold for performing a total thyroidectomy as opposed to a lobectomy should be lower with regard to the size of the primary tumor within the thyroid gland. Elective lateral neck dissection is not recommended, but clearance of the central compartment even in the absence of gross lymphadenopathy has been favored due to a high incidence of microscopic metastatic disease. However, such an operation is associated with a higher likelihood of recurrent laryngeal nerve injury as well as permanent hypoparathyroidism both of which are complications whose morbidity may be worse than the benign course of differentiated thyroid cancer itself and therefore must be performed only by experts. Presence of gross lymphadenopathy in the paratracheal region necessitates a central compartment clearance. A neck dissection of levels II through V best addresses any gross disease present in the jugular chain or the posterior triangle of the neck.

Most children will require postoperative treatment with radioactive iodine for ablation of residual thyroid tissue and any lymphatic or systemic metastasis. Both lymphatic spread and pulmonary metastasis are more common in children. The majority of these lung metastases are micrometastases that are not easily seen on chest radiographs or even CT scans but become apparent on radioactive iodine scans that are performed after thyroidectomy. Children who are treated with a lobectomy are more

likely to have recurrence compared to those that undergo a subtotal or total thyroidectomy. Differentiated thyroid cancer in children is more prone to recur. Long-term follow-up in children may be more challenging and medical compliance in adolescence and young adults may be suboptimal. Radioactive iodine given postoperatively can reduce the likelihood of recurrence.[195]

The dose of radioactive iodine depends on the initial extent of disease. Adjustments can be made for body size or be based on dosimetry. Generally, a dose of 100 mCi for low-risk patients, 150 to 175 mCi for those with lymph node metastasis, and up to 200 mCi for those with very high-risk disease including large tumors, capsular invasion, extrathyroidal spread of disease, extensive nodal disease, or distant metastasis has been recommended.[199]

Thyroid hormone replacement must be withdrawn for 2 to 3 weeks before radioactive iodine treatment and a low-iodine diet must be adhered to. TSH levels >30 mU/L must be reached prior to the treatment. Alternatively, recombinant TSH can be administered on 2 consecutive days followed 24 to 48 hours later with radioactive iodine.

Adverse effects of radioactive iodine include gastritis presenting as nausea and vomiting, neck pain from soft tissue swelling, and sialadenitis. In the long term, concerns for second primary malignancy, diminished fertility, and pulmonary fibrosis have been raised. A comprehensive analysis recently showed a 25% higher risk than the general population of second primary malignancy in patients with differentiated thyroid cancer whether or not they were treated with radioactive iodine. Radioactive iodine-related second primary malignancy risk was seen only with cumulative doses exceeding 200 mCi.[195] No excess of malformations or cancer have been reported in the offspring of individuals who have been treated with radioactive iodine. There is a higher rate of miscarriage within 1 year of treatment for women receiving more than 100 mCi. Hence, pregnancy should be avoided for 6 to 12 months after radioactive iodine therapy. In males, gonadal damage may occur with multiple administrations, and it has been suggested that sperm banking should be considered in patients who are likely to receive a cumulative dose >370 mCi.[200]

Treatment with radioactive iodine must be repeated in 6 to 12 months if there is remaining residual thyroid or tumor tissue. Suppression of TSH levels with exogenous thyroid hormone levels below 0.1 mU/L although

recommended in adults with nodal or distant metastatic disease must be used with caution in the pediatric age group due to possible adverse effects of prolonged subclinical hyperthyroidism.

Patients must be followed up every 6 months with measurement of basal and stimulated thyroglobulin levels and ultrasound of the neck. A diagnostic whole-body radioactive iodine scan is indicated for patients with lymph node or distant metastasis. Being in remission is defined as having undetectable thyroglobulin levels (<1.0 mcg/L) in the absence of thyroglobulin antibody, no evidence of neck disease by ultrasound and negative diagnostic radioactive iodine scan.

Prognosis with carcinoma of the thyroid is excellent. In a SEER study of patients with thyroid carcinoma <20 years of age diagnosed between 1973 and 2004, survival for papillary carcinoma was found to be 98%, 97%, and 91% at 5, 15, and 30 years, respectively. The figures for follicular carcinoma were similar (96%, 95%, and 92%).[192]

Medullary thyroid carcinoma arises from the parafollicular or C cells within the thyroid gland. It is a rare tumor in the pediatric age group. It results from an activating mutation in the RET proto-oncogene that is dominantly inherited as part of the multiple endocrine neoplasia type 2 syndrome. The sporadic variety of medullary thyroid carcinoma that is common in adults is exceedingly rare in children. MEN2A, consisting of medullary thyroid carcinoma, parathyroid hyperplasia, and pheochromocytoma, is by far the more common, occurring in 90% to 95% of the childhood MEN2 cases. Familial MTC is thought to be a variant of MEN2A and is diagnosed when medullary thyroid carcinoma occurs in multiple generations without any parathyroid hyperplasia or pheochromocytoma. MEN2B is the rarer form and is characterized by early development and an aggressive course of medullary thyroid carcinoma. The syndrome includes pheochromocytoma, Marfanoid habitus, pectus excavatum, hypotonia, mucosal neuromas of the lips and tongue, and ganglioneuromatosis of the intestine and urinary tract.[201,202]

In childhood, medullary thyroid carcinoma occurs with equal frequency in boys and girls. It is the most common thyroid malignancy in children younger than 5 years of age. In the era of genetic testing, it is uncommon for a child to present with clinical disease. Presymptomatic identification of RET mutation is the predominant mode of presentation. Mutations in the RET

proto-oncogene have been categorized into American Thyroid Association risk levels A through D according to an increasing risk of aggressive medullary thyroid carcinoma (see Table 5 in Kloos et al.[201]). MEN2A is most frequently caused by mutations in RET exons 10 (codons 609, 611, 618, and 620) and 11 (codon 634). MEN2B is almost always caused by mutation in exon 16 (codon 918).

Surgery is the mainstay of treatment of medullary thyroid carcinoma. The best hope of cure is before any metastasis has occurred. Patients with medullary thyroid carcinoma must have a baseline calcitonin level measured. If calcitonin is <100 pg/mL, the size of the primary thyroid nodule will be less than a centimeter in 98% of the patients. Systemic metastases are strongly associated with a markedly elevated calcitonin level (>5,000 pg/mL) but have been detected in patients with levels as low as 150 pg/mL. CEA levels are also associated with disease status.[203]

Prophylactic thyroidectomy is recommended in children with a known germline mutation in the RET proto-oncogene. Timing of prophylactic thyroidectomy is best guided by the ATA risk level of the RET mutation (see Table 6 in Kloos et al.[201]). Infants with ATA-D (codon 918) mutation must undergo a total thyroidectomy as soon as possible within the first year of life, whereas those with ATA-C (codon 634) mutation must have this surgery before 5 years of age. For children with ATA-A and ATA-B mutations, surgery may be delayed beyond 5 years of age in the setting of normal annual serum calcitonin level, normal ultrasound of the neck, family history of a less aggressive medullary thyroid carcinoma, and family preference.[201] All prophylactic thyroidectomy surgery should be performed in expert hands at experienced tertiary care centers.

In patients with biopsy-proven medullary thyroid carcinoma, calcitonin levels must be obtained prior to surgery. For patients with levels below 400 pg/mL, ultrasound imaging of the neck must be performed to rule out metastatic disease in the lymph nodes. For those with levels higher than 400 pg/mL, imaging must include CT scan of the chest and abdomen as well as a contrast-enhanced MRI of the liver to rule out systemic metastasis.[203]

A total thyroidectomy with central compartment neck dissection is required for patients whose disease is limited to the thyroid gland. No added value has been demonstrated for elective lateral neck dissection in the

absence of discernible disease outside the central compartment. However, a lateral neck dissection must be performed if metastatic disease can be demonstrated in the lymph nodes of the jugular chain or in the posterior triangle of the neck by imaging or confirmed by biopsy. Patients with spread of disease in the mediastinal lymph nodes may benefit from surgical clearance for palliation or prevention of tracheal compression but will rarely achieve biochemical remission.

Although there are some retrospective case series that showed benefit, there are no strong data in support of the use of radiation therapy postoperatively in high-risk disease. Cytotoxic chemotherapy has generally not been found to be of benefit with medullary thyroid carcinoma. Recently, vandetanib, a RET kinase inhibitor, was approved for use after it showed prolongation of progression-free survival in a randomized study.[204]

The prognosis of patients diagnosed with medullary thyroid carcinoma is dependent on the extent of disease at the time of presentation. When the initial disease is limited to the thyroid gland, survival at 10 years is ~95%. With lymph node involvement at presentation, the 10-year survival is closer to 75%, whereas in cases with distant metastatic disease, it drops to 40%.[203] The mean duration of survival for those treated for medullary thyroid carcinoma diagnosed in childhood was 28.3 years in one study of SEER data.[203]

Calcitonin levels are measured initially at 6 months after surgery and then every 6 months for the first 2 to 3 years. More frequent measurements may be necessary if calcitonin level starts to rise. Frequency of estimation then depends on the estimated calcitonin doubling time.

Parathyroid Carcinoma

Although exceedingly rare, parathyroid carcinomas have been reported in the pediatric literature. It requires upfront en bloc resection for cure with avoidance of rupture of the tumor capsule, rather than a simple parathyroidectomy as one would pursue for a benign adenoma. As diffuse metastatic progression renders patients incurable with refractory hypercalcemia and chronic hyperparathyroidism, early consideration and management by specialist teams is mandatory, particularly for cases with significant elevation of calcium and parathyroid hormone or with atypical

adherence of tumor to surrounding structures.[205,206]

Melanoma

Although melanoma is rare in children, accounting for only 1% to 4% of all melanomas, it is still the most common solid tumor in the 15- to 29-year age group. Approximately 450 new cases are diagnosed in individuals younger than 20 years of age in the United States each year.[207,208] The incidence of melanoma is increasing in the United States in children and adolescents. Most children with the disease are at least 10 years of age.[209]

The disease is more common in the Caucasian race but children with melanoma who are younger than 10 years of age are ethnically more diverse.[209] The risk of melanoma increases with an increased number of benign melanocytic nevi and atypical nevi. Giant congenital nevi are associated with a greatly increased risk of melanoma.[208] A positive family history of melanoma also increases the risk of developing this cancer. Mutation in the MITF gene predisposes to both familial and sporadic melanoma. Individuals with dysplastic nevus syndrome have a cumulative lifetime risk of up to 100%. Mutations in BAP-1 as well as germline mutations in CDKN2A and CDK4 have been found in familial melanoma. Gain of KIT and loss of INK4A have been frequently noted in pediatric melanoma.[210] Extrinsic UV radiation exposure with indoor tanning is an important risk factor for melanoma in adolescents, and many states are developing legislation banning the use of tanning salons by minors.

Melanomas in children do not always follow the established criteria of asymmetry, border irregularity, color variegation, diameter larger than 6 mm, and evolution (ABCDE). It has been shown that many lesions are amelanotic and present with bleeding, bumps, and color uniformity. Hence, it is important to have a higher index of suspicion in children with skin lesions.[211] A full-thickness excisional biopsy is the procedure of choice for establishing the diagnosis. A higher proportion of children with melanoma have thicker tumors and positive lymph node metastasis at the time of presentation than is seen adults.[212]

Margins of excision of 1 cm around the primary lesion are adequate for treatment of thin (<1 mm) melanomas. Margins of 1 to 2 cm are recommended for treatment of melanomas that are 1 to 2 mm thick. For

melanomas thicker than 2 mm, margin of 2 cm is considered adequate.[213]

Children with melanoma can benefit from sentinel lymph node biopsy.[212,214] Routine use of sentinel lymph node biopsy is not recommended for thin (<1 mm) melanomas as the incidence of metastatic lymphadenopathy is low. However, a subgroup of patients with ulceration or mitosis (one or more per high-power field) may benefit from sentinel lymph node biopsy. Patients with intermediate-thickness melanoma (1 to 4 mm) stand to benefit the most from sentinel lymph node biopsy. The procedure helps identify patients with occult lymphatic metastasis whose outcome is improved significantly due to early identification and treatment with completion lymphadenectomy.[215] Because patients with thick melanomas (>4 mm) are at high risk for systemic metastasis, historically, sentinel lymph node biopsy has not been offered because of lack of a demonstrated survival benefit. However, if distant metastasis is not present, these patients can be managed similarly to those with intermediate-thickness disease and hence are frequently offered a sentinel node biopsy. Lymphoscintigraphy must be performed to identify sentinel nodes as well as any in-transit nodes both of which must be removed. Patients with sentinel lymph nodes demonstrating metastatic melanoma should undergo a completion lymphadenectomy.[213]

Fine needle aspiration cytology must be performed if regional lymphadenopathy is noted clinically or radiologically. Confirmed metastatic melanoma is best treated with a comprehensive neck dissection. For melanomas arising on the face and scalp, a superficial parotidectomy may be included with neck dissection for complete clearance of draining lymphatics.

The survival of patients with melanoma in the pediatric and adolescent age group is similar to that in adults and is associated with tumor thickness, ulceration, lymph node status, and overall stage. There is a trend toward increased survival in children younger than 10 years of age.[207] The 10-year overall survival was reported to be 94.1% for American Joint Committee stage I disease, 79.6% for stage II disease, and 77.1% for stage III disease in an analysis of 365 pediatric patients with melanoma in an international registry study.[207]

Patients with advanced disease can benefit from recent advances in therapy including vemurafenib and ipilimumab. However, the data regarding use of these agents in the pediatric age group are still lacking.

Nonmelanoma Skin Cancer

Nonmelanoma skin cancer is exceedingly rare in the pediatric age group. Xeroderma pigmentosum is a rare autosomal recessive disorder that appears in early childhood and is characterized by photosensitivity, hyperpigmentation, and premature skin aging.[216] Patients are at increased risk for both squamous cell carcinoma and basal cell carcinoma. Face, head, neck, scalp, and other sun-exposed areas are common locations.[217] Ionizing radiation for treatment of previous childhood malignancy is also a known risk factor although cancers most commonly develop in early adulthood.[218]

Nevoid basal cell carcinoma syndrome is an autosomal dominant disorder that is characterized by multiple jaw keratocysts and basal cell carcinomas. Many patients have a recognizable appearance with macrocephaly, forehead bossing, and coarse facial features. Basal cell cancers develop more commonly from the third decade onward.[219] The primary underlying disorder is a defect in hedgehog signaling. Vismodegib, a hedgehog pathway inhibitor, has been shown to reduce the basal cell carcinoma tumor burden and block the growth of new basal cell carcinomas in patients with this condition. However, adverse events associated with treatment, including loss of taste, muscle cramps, hair loss, and weight loss, have led to discontinuation in over half of treated patients.[220]

Squamous Cell Carcinoma of the Upper Aerodigestive Tract

Squamous cell carcinoma of the oral cavity and other mucosal locations in the upper aerodigestive tract is an uncommon condition in children and adolescents. A literature review documented 55 cases in the period from 1894 to 2011 in the United States.[221] Predisposing conditions include xeroderma pigmentosum, Fanconi anemia, epidermolysis bullosa, and juvenile respiratory papillomatosis.

Fanconi anemia is a rare recessive DNA repair disorder that causes progressive bone marrow failure and is associated with a high incidence of malignancies including acute myeloid leukemia and squamous cell carcinoma of the head and neck.[222] Head and neck squamous cancers occur at an incidence several hundred to thousand folds higher than the normal

population. Cancers can develop anywhere in the upper aerodigestive tract and are characterized by a more aggressive behavior including a higher likelihood of soft tissue invasion and lymphatic metastasis. The most frequent birth defects in Fanconi anemia include skin hyperpigmentation, café au lait spots, short stature, and abnormalities of the head, eyes, kidneys, and ears. Because many patients with Fanconi anemia may be phenotypically normal, any patient who is diagnosed with a squamous cell carcinoma of the head and neck in the pediatric age group should be considered for testing for this condition with a chromosomal breakage test.[223] The mainstay of therapy is surgery because these patients are unusually sensitive to the toxic effects of radiation and chemotherapy. Severe mucositis and pancytopenia commonly occur and can lead to further complications including bleeding and infection.[224]

Malignant Germ Cell Tumor

Malignant germ cell tumors arise from primordial germ cells and afflict ~300 children annually in the United States.[225] The etiology of these tumors remains to be fully elucidated, although aberrant embryonal primordial germ cell migration is one of several hypotheses for the origin of these tumors (Brown 1976). The combination of platinum-based chemotherapy and surgery is most frequently employed, and current survivorship approaches 80% to 90% at 3 years, particularly when high-dose chemotherapy regimens are used.[226,227] Unfortunately, the intensification of chemotherapy agents, although lifesaving, also induces a variety of toxicities.[228]

Teratoma is a nongerminomatous germ cell tumor found particularly in neonates. Most teratomas are benign, with an overall malignancy rate of 20%, varying greatly depending on the primary site.[229] Mature or immature teratoma of children frequently demonstrates a benign long-term outcome.[230] Approximately 5% of head and neck teratomas contain malignant elements; these are rare in neonates and occur primarily in adults.[231] Other malignant germ cell tumors include embryonal carcinoma, endodermal sinus tumor/yolk sac tumor, choriocarcinoma, polyembryoma, and gonadoblastoma. Mixed tumors combine various components of the array of germinomatous and nongerminomatous germ cell tumors, but the natural history is driven by the more malignant component(s), as is the therapy.

Lesions in the head and neck region account for ~5% of all benign and malignant germ cell neoplasms[232]; common sites include the neck, oropharynx, nasopharynx, orbit, and paranasal sinuses.[233,234] Oropharyngeal and nasopharyngeal teratomas occur almost exclusively in neonates and young infants. Teratomas have a predilection for the oropharynx.[234] Orbital teratomas also typically present at birth with proptosis. The ovaries, testes, anterior mediastinum, retroperitoneum, and sacrococcygeal region are the most common primary sites outside the head and neck.

Even though the vast majority of pediatric cervical teratomas are histologically benign, the morbidity and mortality associated with these tumors can be significant.[235] Infants with large cervical teratomas have an increased incidence of polyhydramnios, prematurity, and stillbirth.

Histologically, teratomas are composed of ectodermal, mesodermal, and endodermal components. Depending on the degree of differentiation of the components, teratomas are classified as mature or immature. A predominance of immature elements portends a poorer prognosis and may suggest malignancy.[236] This, however, is not true in the neonatal age group. Teratoma secretion of alpha-fetoprotein and beta-human chorionic gonadotropin has implications regarding postoperative monitoring.

The treatment of teratomas is surgical extirpation, frequently in conjunction with chemotherapy. Because malignant degeneration in teratomas of the head and neck among children is so rare, much of the experience in the therapy of pediatric germ cell malignancies has been achieved in treating these lesions in gonadal and other extragonadal locations. These cases are primarily managed with resection. For those with unresectable or metastatic disease, chemotherapy is effective, thereby obviating maximal resection upfront when intervention risks damage to vital normal tissues. Patients with unresectable or residual disease may also receive radiation to the primary site; however, this is rarely advisable for infants.[237] Metastasis from childhood teratomas is rare, although it has been reported. When systemic metastases are present, multiagent chemotherapy and surgical resection are suggested. Salvage chemotherapy is used in the setting of recurrent disease.[236]

Almost all patients demonstrate an initial response to therapy. After surgical resection of immature teratomas, the 3-year survival is 93%.[236]

Orbital teratomas have an excellent prognosis after orbital exenteration.[235] The 4-year disease-free survival of malignant and mixed teratoma is ~70%.[238]

Regardless of the histopathology of the tumor, all patients should be followed for possible recurrence. Oropharyngeal and nasopharyngeal teratomas may require follow-up endoscopic examinations. Radiologic follow-up by means of CT or MRI is typically appropriate (April 1998). The tumor-secreted products alpha-fetoprotein and beta-human chorionic gonadotropin should also be monitored.

Paraganglioma

Paragangliomas and pheochromocytomas are rare, morphologically identical neuroendocrine tumors, with pheochromocytoma designating those that arise from the adrenal medulla, whereas paragangliomas are those that arise in various locations extra-adrenally along the parasympathetic and sympathetic chain. Most paragangliomas of the head and neck are nonsecreting (nonfunctional) tumors from parasympathetic tissues.[151] Approximately a quarter of paragangliomas are associated with a hereditary predisposition syndrome, with key genetic syndromes including multiple endocrine neoplasia, von Hippel-Lindau, neurofibromatosis type 1, hereditary paraganglioma syndrome, and Carney triad.[12,151] Due to the general potential for spontaneous or induced paroxysmal excess catecholamine release in turn leading to sequelae such as hypertensive crises, appropriate biochemical evaluation and multidisciplinary preoperative management with consideration for preprocedural blockade are mandatory. Biochemical diagnosis may be typically made with plasma and urine fractionated metanephrines. Different succinate dehydrogenase (SDH) mutations are implicated in different typical clinical manifestations, with paraganglioma of the head and neck often associated with SDHB, SDHD, and SDHC, with the latter particularly associated with multiple tumors of the head and neck.[11,12,239,240] Young patients with SDHB mutations may have an associated higher rate of metastatic presentation.[151,239] Special functional imaging techniques, such as FDOPA (18F-fluorodopa) PET, may allow increased sensitivity for head and neck paragangliomas that may at times be missed on conventional octreotide scintigraphy.[12] All pediatric patients with paragangliomas of the head and neck should be considered for genetic counseling and evaluation, with

engagement of the family and the multidisciplinary team in management decision-making.[239–242]

Tracheal and Endobronchial Tumors

Very rarely, pediatric tracheal and intrabronchial tumors may be identified, with diagnoses including well-differentiated neuroendocrine tumors (“carcinoid tumors”) and mucoepidermoid carcinoma.[243–245] Endobronchial presentation of the tumors highlighted above, including inflammatory myofibroblastic tumor and non-Hodgkin lymphoma, have also been reported.[244,246]

NUT Midline Carcinoma

NUT midline carcinoma represents a very rare malignancy, characterized by rearrangement of the NUT gene on chromosome 15q14.[151] First described in pediatric patients but affecting patients of all ages, these aggressive tumors characteristically occur in midline epithelial sites, including the mediastinum and upper aerodigestive tract. Despite aggressive multimodality therapy including surgical resection and radiation therapy, current fatality rates remain high, and ongoing studies are warranted to improve the course of this malignancy.[247,248] An international NUT midline carcinoma registry[249] has been established in an effort to promote advances.

SPECIAL CONSIDERATIONS

Genetic Considerations

Family history should be carefully reviewed in all children with cancers of the head and neck. Decision-making regarding genetic testing should be considered carefully with families as well as pediatric patients as developmentally appropriate, in the context of pre- and posttesting counseling, as recommended by the American Society of Clinical Oncology.[250] A number of cancer predisposition syndromes with potential manifestations in the head and neck in children have testing protocols or guidance considerations to help implement individualized decision-making, including retinoblastoma, von Hippel-Lindau syndrome, multiple endocrine

neoplasia, familial paraganglioma syndrome, PTEN hamartoma tumor syndrome, and Li-Fraumeni syndrome.[241,251–253]

Pediatric Cancers in Resource-Limited Settings

The epidemiology of cancers of the head and neck in the pediatric population is quite distinct in many resource-limited settings globally, compared to that in North America and other developed areas. In equatorial Africa, for instance, 50% of pediatric cancers are lymphomas, due to the predominance of endemic Burkitt lymphoma.[142,254] In contrast to sporadic Burkitt lymphoma, endemic cases most often present with jaw swelling or periorbital swelling.[254] Although Kaposi sarcoma represents 78% of oral cavity sarcomas in adults in the United States,[4] it is not typically a diagnosis encountered in children in North America, but is a dominant concern in settings with endemic HIV, including in Africa. Children with Kaposi sarcoma may present with manifestations in the head and neck such as brawny and disseminated lymphadenopathy, multifocal oral, facial, scalp, or tracheal lesions and nodules.[255]

Masses in the neck in children typically present late and with more advanced disease in resource-limited settings.[254,256] Local health beliefs are among potential factors for delayed presentations or alternative therapy choices, including those involving African traditional healers.[256] Tuberculous adenopathy, particularly in regions with endemic tuberculosis, needs to be considered as a potential comorbid or primary condition for a mass in the neck in a chronically ill child.

Although the survival of children with cancer has dramatically improved in recent decades, unfortunately, for the 80% of children in the world with cancer who live in low- and middle-income settings, outcomes are significantly poorer.[35,257] Apart from potentially distinct disease epidemiology and infectious comorbidities such as HIV and endemic tuberculosis, physicians working in many resource-limited settings are confronted with shared concerns regarding access to quality diagnosis, treatment, and care, with health system and service delivery challenges, human resource and technology gaps, and sociocultural factors. Thus, effective diagnosis and management of a mass in the head and neck warrant considerations of an effective chain of care, from preoperative management

of infections through to safe anesthesia and intensive care, alongside appropriate handling of tissue specimens and care coordination among trained team members, feasibility of local control including access to complex surgery and radiotherapy, and timely delivery of multimodality therapy.[258,259]

Compounding late and advanced presentations, children in these resource-limited environments often have less functional reserve to tolerate treatment owing to poor nutrition or health status and less access to essential diagnostic tools, medications, and interventions due to prohibitive costs and/or regulatory barriers. Outcomes in resource-limited settings even for typically curable cancers are thus limited by high rates of progressive disease, treatment- and infection-related morbidity and mortality, as well as treatment refusal and treatment abandonment (the failure to complete curative therapy).[254,259,260] As an example, whereas almost all children with retinoblastoma diagnosed in high-income settings survive, children with retinoblastoma diagnosed in many resource-limited settings have cure rates much below 50%, warranting sustained partnered approaches that are sensitive to contextual health systems needs and social determinants of health.[261,262]

Context-sensitive, locally relevant evidence and best practices should be sought and applied wherever possible, extending clinical studies as well as interval consensus recommendations for specific cancers as well as supportive care, via networks such as the Pediatric Oncology in Developing Countries working groups of the International Society of Paediatric Oncology (SIOP).[254,255,260,263–266] Consensus publications for pediatric cancer care in resource-limited settings have included adapted treatment regimens and recommendations for diagnoses such as retinoblastoma[266] and Kaposi sarcoma,[254] as well as position statements on core needs including supportive care,[265] nursing care,[264] and addressing treatment abandonment.[260] Through extended partnerships and sustained on-site interdisciplinary efforts, continued progress is being made so that children with cancers of the head and neck the world over may benefit from diagnostic and therapeutic advances.[261,267,268]

OPTIMIZING LONG-TERM

OUTCOMES

Reconstruction of Defects in the Head and Neck

The idea of using flaps of local tissue to reconstruct adjacent defects led to significant advances in reconstructive surgery. Initially, flaps were selected randomly based on criteria such as proximity to a soft tissue defect and geometry rather than on specific knowledge of the pattern or reliability of the blood supply.[269] Subsequently, axial flaps such as the deltopectoral flap and the groin flap were described, based on an incorporated known axial blood supply. Myocutaneous flaps were added to the list of available flaps in the 1970s, and this improved the facility with which immediate reconstructions were reliably performed. Free microvascular tissue transfer is now routinely used in reconstructive surgery.

Reconstructive microsurgery has become an integral part of head and neck reconstruction, allowing the completion of complex resections with predictable outcomes. Common flaps and their reconstructive applications include (but are not limited to) ones listed in **Table 24.10**.

Table 24.10 Recontructive Options for Surgical Defects in the Head and Neck

Flap	Defect
Anterolateral thigh	Floor of mouth, tongue, face, skull base, maxilla, mandible (soft tissue only)
Radial forearm	Floor of mouth, tongue, face, palate
Scapula	Face, maxilla, mandible
Fibula	Mandible, maxilla, calvarium
Rectus abdominis	Skull base, maxilla
Latissimus dorsi	Scalp

Surgery for cancer of the head and neck is rare in the pediatric age group,

and there are limited reports in the literature regarding reconstruction of these defects. Despite these limitations, some general observations with regard to indications for free flap reconstruction, needed for surgical planning to incorporate future facial growth and dental rehabilitation, have been made. Future advances with newer alloplasts, virtual surgical planning, and distraction osteogenesis will no doubt improve treatment of these patients. In general, pediatric patients lack the numerous comorbid conditions of adult head and neck cancer patients (e.g., tobacco use, vascular disease), thus making reconstruction more successful. Given the pediatric patient's improved capacity for nerve healing, current and future research is focused on improving outcomes using innervated free flaps to improve sensibility and function.

General discussions about principles of head and neck reconstruction and techniques can be found elsewhere in this text. Thus, the following discussion is focused on issues specifically relevant to pediatric head and neck cancer reconstruction in the pediatric age group.

Mandible

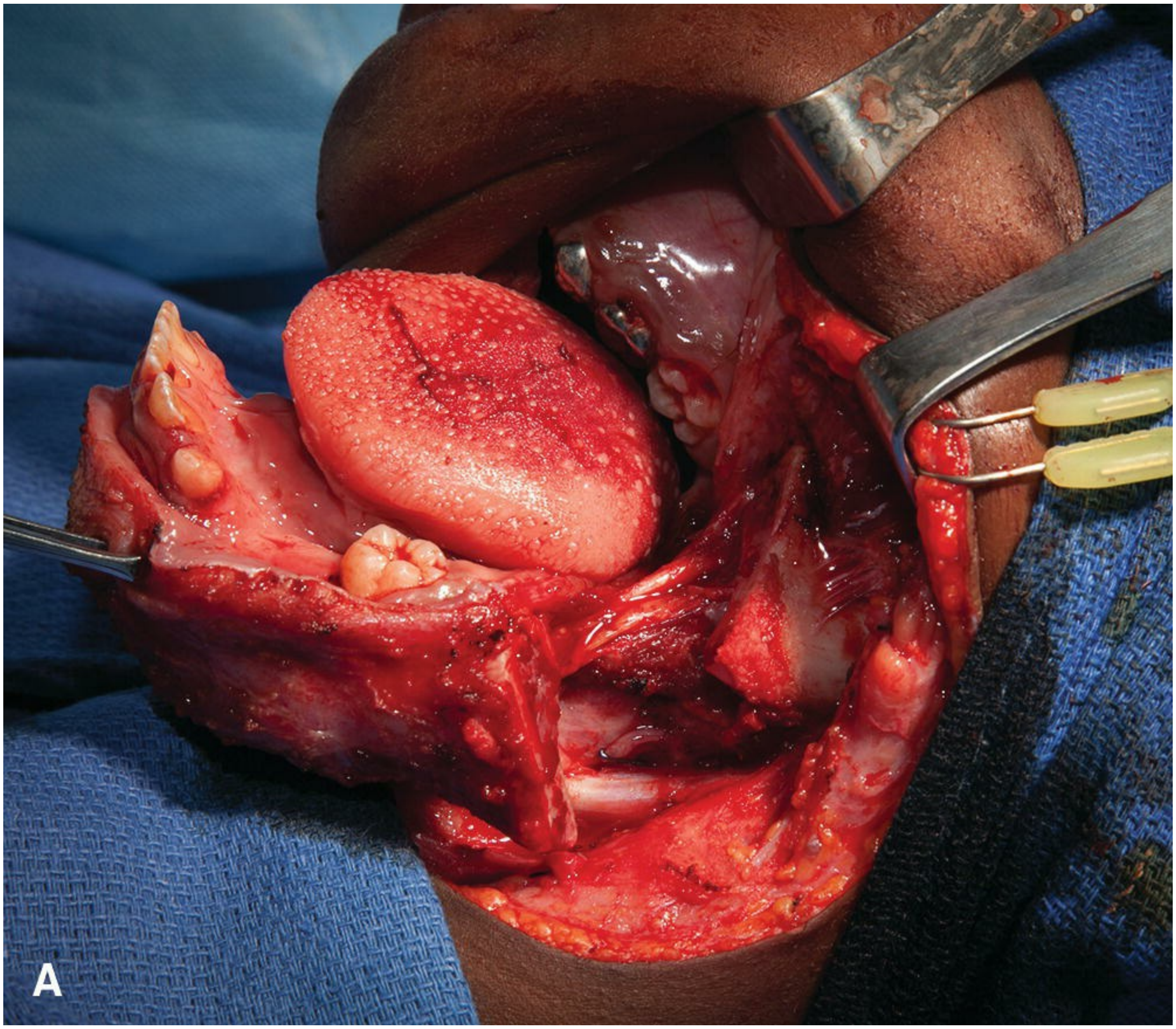
Many techniques have been used in reconstructing the mandible, including those associated with nonvascularized bone grafts, sterilized autogenous bone, and alloplasts of different types. Although there may be specific indications to use some of these techniques, the goal of reconstruction must include control of the malignant process and reconstitution of form, function, and cosmesis. The issue of whether or not reconstruction with bone is always required in reconstructing mandible is particularly challenging in pediatric patients.[270] In many situations, posterior and lateral mandibular defects can be reconstructed with a soft tissue flap only, without the use of a plate or bone. Although short- and midterm outcomes, with regard to function and cosmesis, are acceptable, the greatest disadvantage is that, over time, progressive mandibular crossbite and malocclusion develops and dental restoration is either impossible or severely compromised. The consensus would appear to be that this is a reasonable option for lateral mandibular defects in patients with multiple comorbidities and/or a poor prognosis.

The criterion standard for reconstruction of the mandible using the fibular osseocutaneous flap, originally introduced by Hidalgo in 1989.[271] It provides good bone stock for fashioning a mandible, and the option of a reliable skin

paddle that can be used either for oral lining or external cover with the potential for reinnervation. Among the several advantages of the fibular osseocutaneous flap is the fact that the bone stock it supplies is adequate for insertion of osseointegrated implants for dental rehabilitation. This is important for restoring oral function although, because of cost issues, many patients, particularly in North America, are not in a position to benefit from this final step in their reconstruction. A modification of the fibular flap that provides a greater mandibular height and optimizes dental rehabilitation is to double barrel the fibula.[272,273]

With regard to pediatric patients, there are a number of unique concerns with regard to mandibular reconstruction. When reconstruction is performed in a skeletally immature patient, it is important to attempt to avoid the mandibular growth centers in the condyle and symphysis; otherwise, growth retardation will ultimately necessitate surgical revision, as with bone reconstruction in the extremities.[274] Similarly, hardware (i.e., plates and screws) must avoid these areas.

Reconstruction with a free flap is a challenging but reliable option in pediatric patients (**Fig. 24.13**). Preoperative planning should involve oral maxillofacial surgeons and take into consideration the timing of tooth development and maxillary and mandibular growth as part of the long-term strategy.[275] Growth of the vascularized fibula without epiphyseal transfer has not been identified. Therefore, there are often needs for additional osteotomies to readvance the fibula or for additional vascularized or nonvascularized bone grafts. Also, to ultimately have enough bone stock for implants, double-barrel fibular flaps or secondary bone grafts are often necessary. Many of these patients need more than one free tissue transfer of bone and soft tissue before their reconstruction is completed at the time of skeletal maturity.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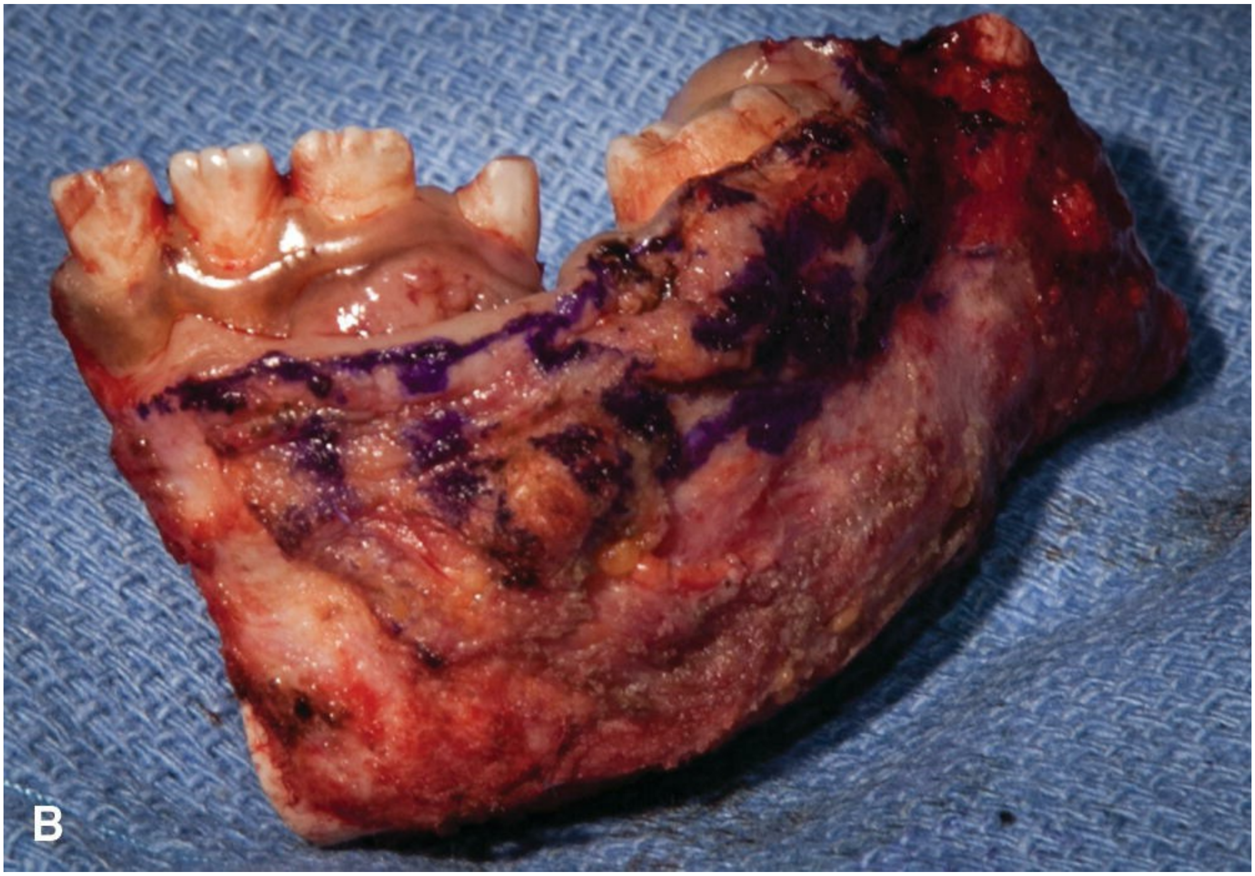

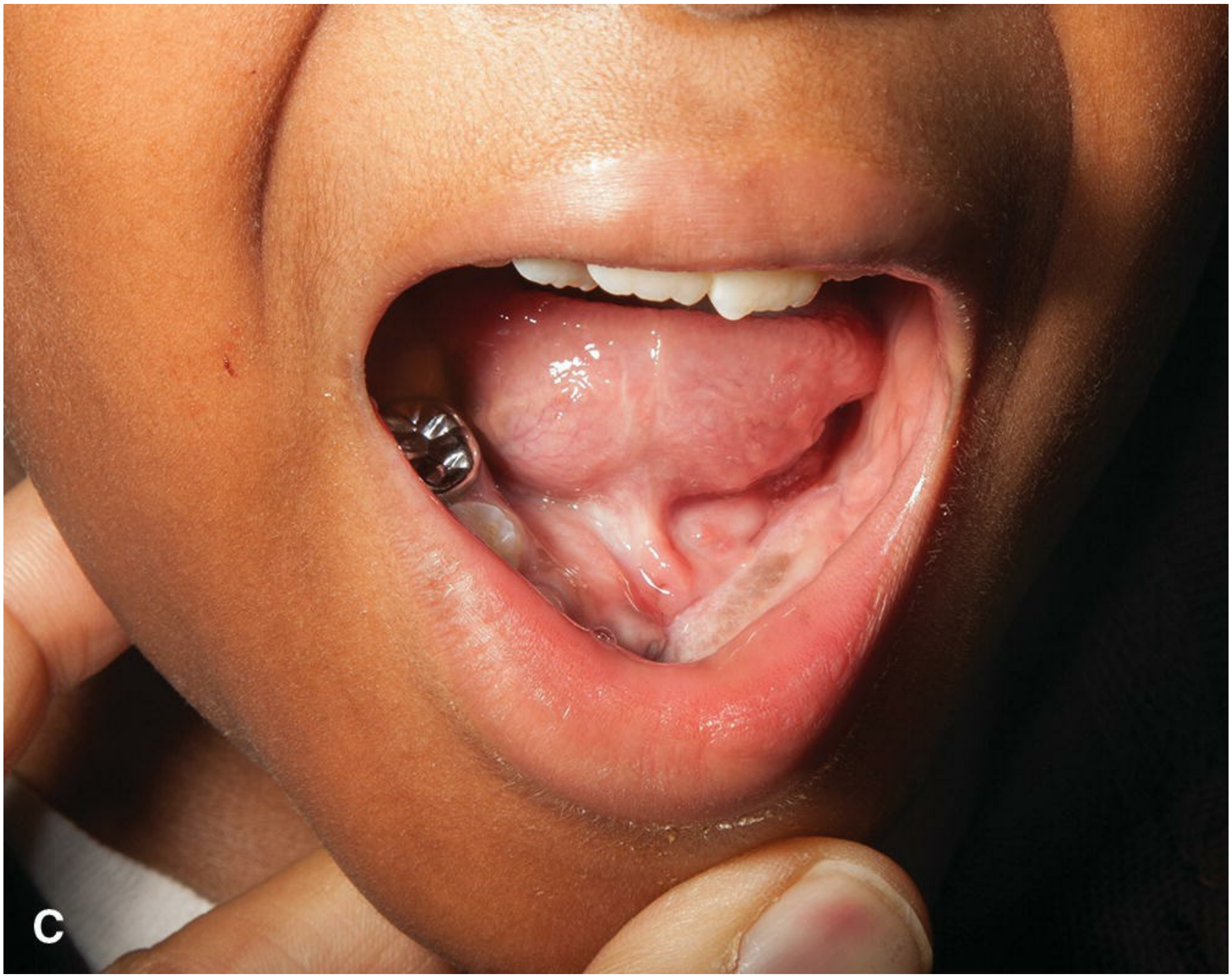
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Figure 24.13. A: A 6-year-old boy with an invasive gingival squamous

carcinoma undergoing segmental mandibulectomy. **B:** Mandibulectomy specimen. **C:** Intraoral appearance after fibula reconstruction. **D:** Appearance after reconstruction.

It should be noted that in extremely young (i.e., <2 years) or small patients, prosthetic-only reconstructions (e.g., reconstruction plate; alloplastic stainless steel mandible prosthesis) are viable options, provided that there is ultimately a plan for bone grafting. Similarly, traditional nonvascularized bone graft mandibular reconstruction has been successful in the pediatric population, but is not as reliable as free flap reconstruction.

Although dental rehabilitation is a necessary part of recovery after cancer of the oral cavity, there is no consensus regarding the type or timing of dental rehabilitation in the pediatric patient. Options include no reconstruction, denture or fixed prosthesis reconstruction, or placement of osseointegrated dental implants. Dental implants have the advantage of permanent fixation for a dental prosthesis and help to prevent long-term osteolytic changes of the native mandible and fibular flap by transferring loading directly to the bone. However, owing to growth changes in the pediatric native mandible and maxilla, it is not a feasible option in many children. Dentures and/or a fixed prosthesis (bridge) may be a viable option in these patients, but they do not provide an adequate stress response to the mandible and thus can ultimately result in significant bone loss with the need for future bone grafting and/or flap reconstruction.

Scalp

Although there are many situations in which local flaps can be used to reconstruct the scalp, for larger defects, free flaps are commonly used. Unfortunately, there is no flap available that can replicate the hair-bearing characteristics of the scalp. Also, the surface area of the reconstruction frequently demands a large flap. For these reasons, the general consensus for reconstruction of the scalp is the latissimus dorsi muscle flap, covered with an unmeshed split-thickness skin graft.[276,277] Although the muscle may be bulky initially, the flap generally thins owing to muscle atrophy and ultimately replicates a normal hairless scalp within a matter of months. Of particular importance to the pediatric population, long-term reconstruction of hear-bearing skin requires the use of follicular micrografting, serial excision,

or tissue expansion of hair-bearing residual scalp.

Midface

An area of ongoing development is the management of the maxillectomy defect. With respect to palatal reconstruction, functional outcomes are oftentimes equivocal between microvascular reconstruction and an obturator.[278] The need for adjuvant radiation therapy may preclude the use of metallic implants used for rigid reconstruction. Unfortunately, without some type of rigid reconstruction, soft tissue contracture results to extremely difficult or impossible correction of secondary deformities. Definitive dental rehabilitation frequently needs to wait until skeletal maturity, thus placing a premium on the use of removable prosthetics. Fortunately, it may not be necessary to reconstruct all mucosal surfaces with multipaddled skin flaps, as raw muscle surfaces often mucosalize, and sinus cavities can be obliterated. Finally, even for external facial defects, prosthetics can provide a viable option. Where possible, it is imperative to preserve function unless this compromises the ablative procedure. The diversity of flaps used to reconstruct these defects bears testament to the fact that there is no criterion standard in maxillary reconstruction.

The fibula is used extensively and has the advantage of a long pedicle, versatile bone, and soft tissues and is amenable to placement of an implant.[279] However, the fibula can be bulky, and this can have an impact on flap inset. Anastomosis can be performed to the superficial temporal vessels or to the facial vessels, although often a vein graft is required. The scapular flap is a very versatile flap, as it allows the transfer of excellent bone stock with the option of incorporating muscle for soft tissue reconstruction. It also has the advantage of a long pedicle.

A number of factors particular to pediatric reconstruction merit note. Although reconstruction with soft tissue flaps has been the norm in the past, the major disadvantage of soft tissue–only flaps is that they do not address the structural defect that results from bony resection and progressive soft tissue contracture results, which is extremely difficult to address secondarily, particularly in the pediatric patient.[280,281] These reconstructions ultimately contract, and the patient tends to lose facial height and facial projection, with effects on the nose, lips, and orbits. It is not only intuitive but has been shown in the craniofacial literature that if the bony framework is restored, the soft

tissues cannot contract and the long-term aesthetic results are superior.

As with reconstruction of the mandible, bone flaps do not grow with the native maxilla. Thus, there is often a need for bone regrafting as patients mature.[282] Distraction osteogenesis (DO) is an excellent option, in properly selected patients. Historically, adjuvant radiation therapy has been considered a contraindication to DO. However, there is a growing literature to suggest that DO is a viable option in properly selected patients. Our group has had a favorable experience with this technique, when it is coupled with use of preoperative and postoperative hyperbaric oxygen therapy. Such patients have even successfully tolerated placement of osseointegrated dental implants and bone grafting.

In summary, need for major reconstruction for cancer of the head and neck in the pediatric age group is relatively uncommon, and there are limited reports in the literature regarding reconstruction of these defects. For many reconstructions, no perfect donor tissue is available. In some cases, a patient's ideal donor site has been compromised by trauma, radiation, or progressive comorbid disease. In any event, reconstructive ingenuity is critically important to achieve success in this patient population. Despite these limitations, some general observations with regard to indications for free flap reconstruction, need for surgical planning to incorporate future facial growth, and dental rehabilitation have been made. Future advances with newer alloplasts, tissue engineering, composite tissue allotransplantation, virtual surgical planning, and DO will no doubt improve our treatment of these patients.

Late Effects of Therapy

When discussing late effects of head and neck cancer therapy, the major subcategories include structural or functional abnormalities of normal tissues and secondary malignancies. Although progressive primary tumor remains the overall leading cause of mortality in the majority of these patients, as cure rates improve, growing attention is being focused upon late effects and other causes of morbidity and mortality.[283] Bone growth abnormalities of the craniofacial structures are another manifestation of intensive, multimodality therapy.[284–287] These frequently lead to functional deficits and cosmetic defects; mortality can result in severe clinical scenarios.

The use of surgery to extirpate lesions and/or reconstruct pediatric craniofacial anatomy is not without long-term sequelae. Particularly, when combined with the use of chemoradiotherapy, the late effects can be associated with considerable morbidity. This knowledge continues to drive an extensive array of research into the molecular biology of craniofacial development and surgical reconstruction with the objective of minimization of morbidities.[288–290]

Chemotherapeutic effects cannot be discounted when used as part of a multimodality regimen. The sensitizing potential to enhance toxicity in both tumor and normal tissue is well known.[291] Molecularly targeted agents have sought to selectively enhance tumor cell kill and thereby widen the therapeutic window; however, much remains to be done in bringing effective therapy into the mainstream.[292]

Likewise, a growing body of evidence suggests a small but notable risk of secondary malignancy associated with chemotherapy.[293] The predominant form of these complications arise in the spectrum of myelogenous disorders (myelodysplasia or myelogenous leukemia). There may be a small contribution to the development of solid tumors; however, this has largely been attributed to the frequent concurrent or sequential use of radiotherapy.[294] Still, occasional solid tumor secondary malignancies will develop remotely from the irradiated fields.[295,296]

The increased risk of secondary cancers due to radiotherapy has been well documented, partly due to the longer history of use relative to chemotherapy.[134] Radiotherapy dose reduction may lead to a lower incidence of some secondary solid cancers.[135,297–299] However, at least some data for secondary thyroid malignancy suggest that there may be a threshold effect, beyond which cell-killing effect may predominate over carcinogenesis.[300] The cumulative risk of developing a mesenchymal carcinoma of the soft tissues, thyroid, or head in radiotherapy fields increases over time.[127,296,301] The cumulative risk of developing a secondary malignancy correlates with age of the child, radiotherapy field size, as well as dose; reduction of risks associated with each of these parameters is countenanced while optimizing the chance for cure.

Vascular abnormalities can also be caused as a result of high-dose radiotherapy, and these sequelae may be severe as well.[302,303] The morbidity

and mortality of these late effects remain poorly studied, although initial reports demonstrate the need for improved targeting/selectivity of therapy. The growing array of documented comorbidities associated with therapy is helpful in providing a thorough understanding for the families of pediatric patients, for whom informed consent is a critical process.

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25 Head and Neck Cancer in Developing Countries

Johan Fagan Clare Stannard

INTRODUCTION

Cancer in developing countries is a public health crisis. Developing countries constitute the majority of the world's landmass (**Fig. 25.1**) and are home to more than 50% of its people. Farmer et al.[1] reported in 2010 that developing countries accounted for more than 50% of newly diagnosed cancers and projected that this would increase to 70% by 2030 (**Fig. 25.2**); this increase can be attributed to population growth, reduced mortality from infectious diseases, and an aging society. The same authors report a wide disparity in cancer-related case mortality, which is aligned with income levels of countries, ranging from 75% in low-income countries to 46% in high-income countries (**Fig. 25.3**).[1] Even though developing countries account for 67% of cancer-related deaths, they account for only 5% of cancer-related spending.[1] For all the aforesaid reasons, a discussion about head and neck cancer would be incomplete were it not to include a developing world perspective. It is also apparent that, in order to improve head and neck cancer outcomes globally, it is essential that innovation, expertise, resources, teaching, and research also be directed at addressing cancer in the developing world.

Figure 25.1. Developing (*dark*) versus developed world (*light*).

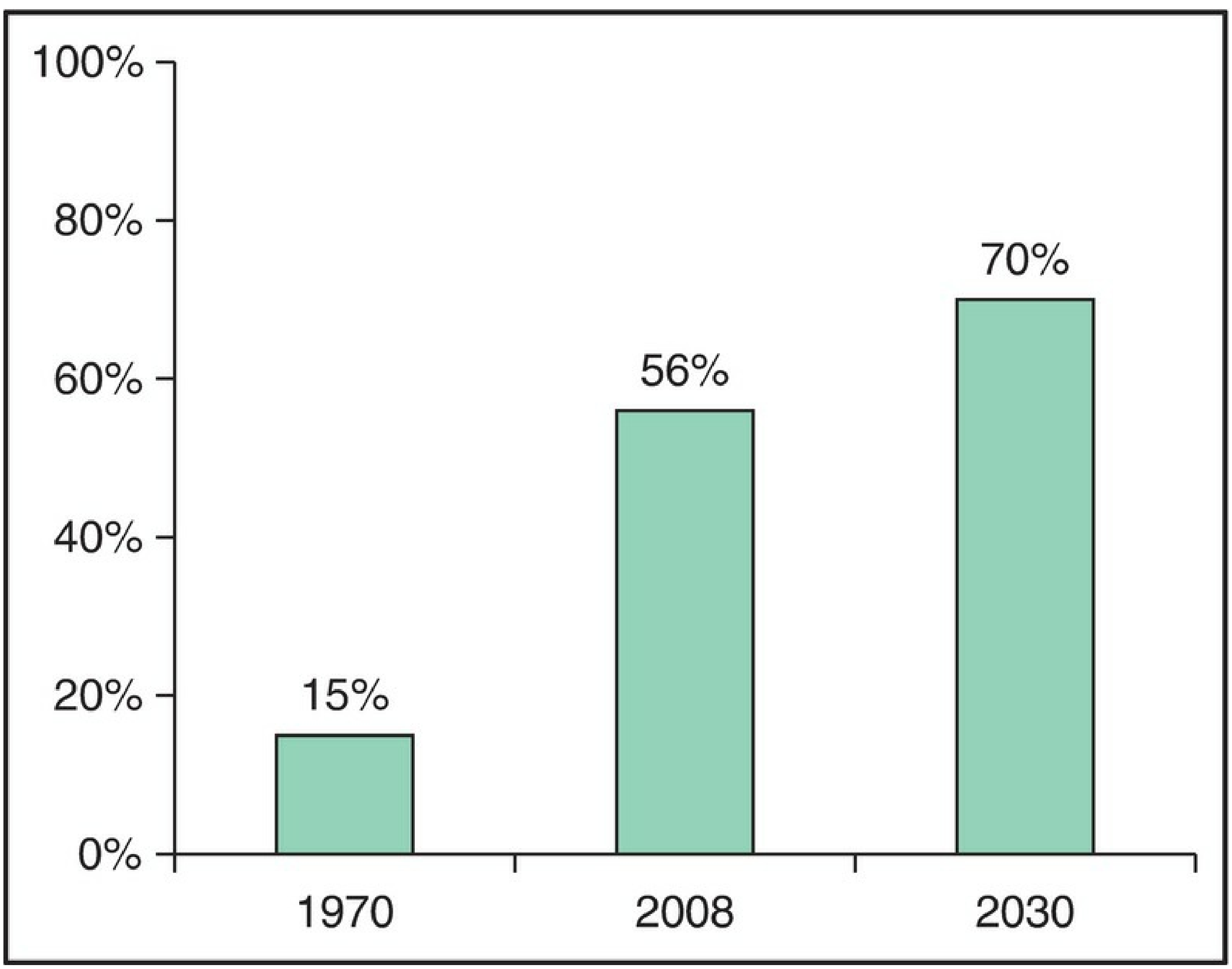

Figure 25.2. Increasing percentage of global burden of cancer in the developing countries. (From Farmer P, Frenk J, Knaul FM, et al. Expansion of cancer care and control in countries of low and middle income: a call to action. *Lancet.* 2010;376(9747):1186–9113.)

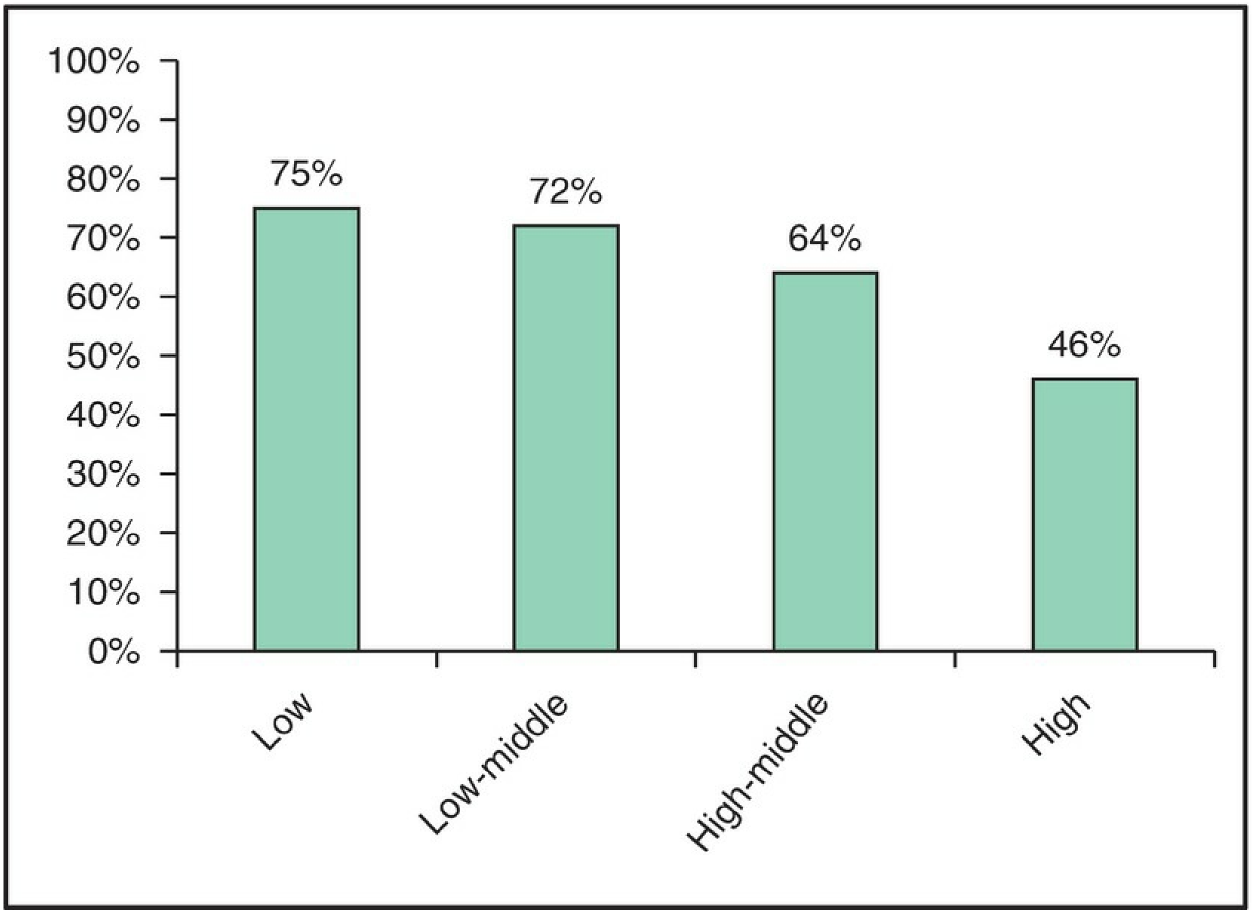

Figure 25.3. Case mortality from cancer according to income levels of countries. (From Farmer P, Frenk J, Knaul FM, et al. Expansion of cancer care and control in countries of low and middle income: a call to action. *Lancet.* 2010;376(9747):1186–9113.)

EPIDEMIOLOGY

The developing world is undergoing rapid economic growth; this is accompanied by lifestyle changes such as increased rates of smoking and alcohol consumption. These changes coupled with increased longevity are associated with global changes in the epidemiology of squamous cell cancer of the head and neck. Two-thirds of oral and pharyngeal cancers (excluding

nasopharynx) occur in developing countries.[2] **Figure 25.4** illustrates the significant geographical variation that exists for the incidence of oral cancer; it is the most common cancer in males in high-risk areas such as Sri Lanka, India, Pakistan, and Bangladesh and accounts for up to 25% of all new cancers.[2] The principal causes of oral cancer are tobacco (smoked or chewed) and betel quid.[2] Buccal cancer is common in Asia due to its association with betel quid and tobacco chewing; 40% of oral cancers in Sri Lanka are buccal carcinomas.[2]

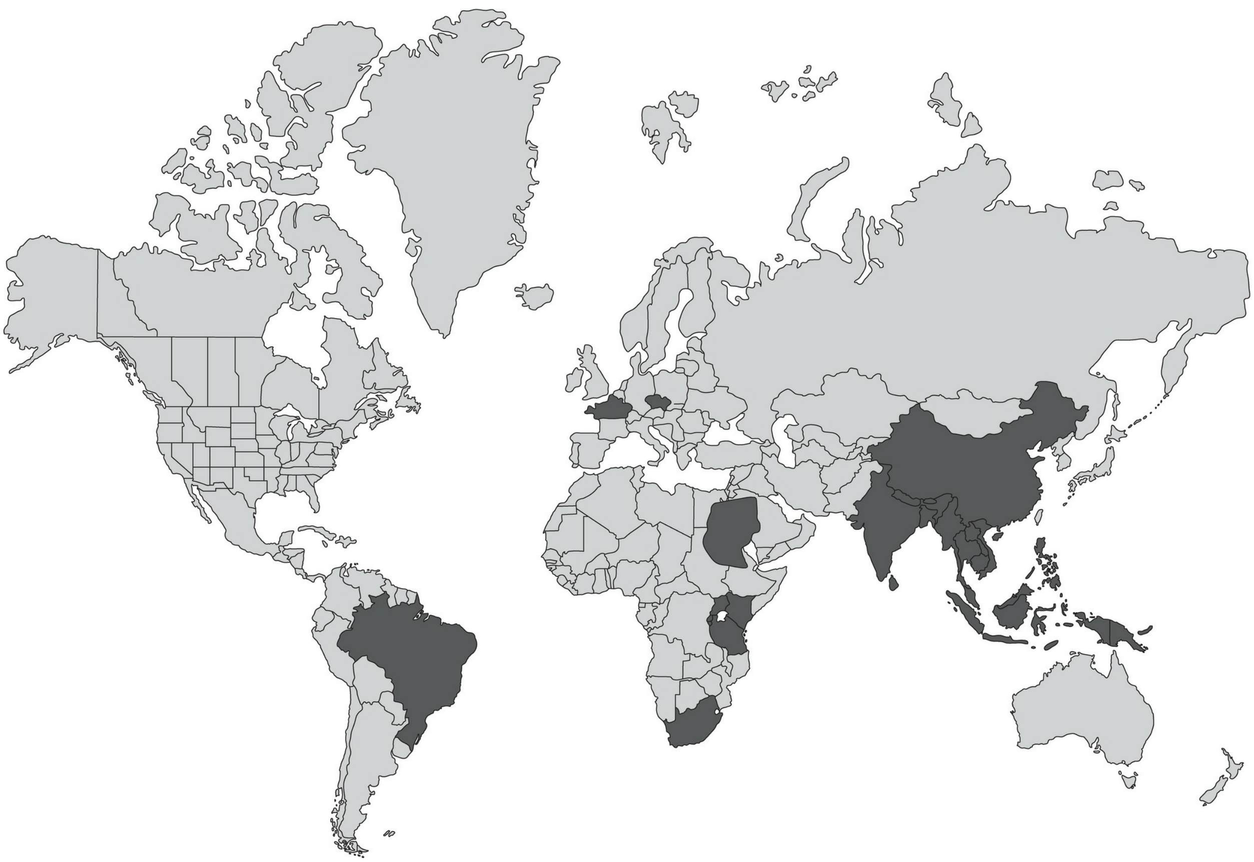

Figure 25.4. Countries with high incidence and mortality from oral cancer. (From Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol.* 2009;45:309–316.)

Cancer of the nasopharynx is also principally a developing world problem (**Fig. 25.5**).[3] It is associated with the Epstein-Barr virus (EBV) in China, Southeast Asia, northern Africa, and the Inuits of Alaska[4] where nonkeratinizing squamous cell carcinoma and undifferentiated carcinoma are more common. Human papillomavirus (HPV) may be an etiologic factor in

the EBV-negative Caucasian population.[5]

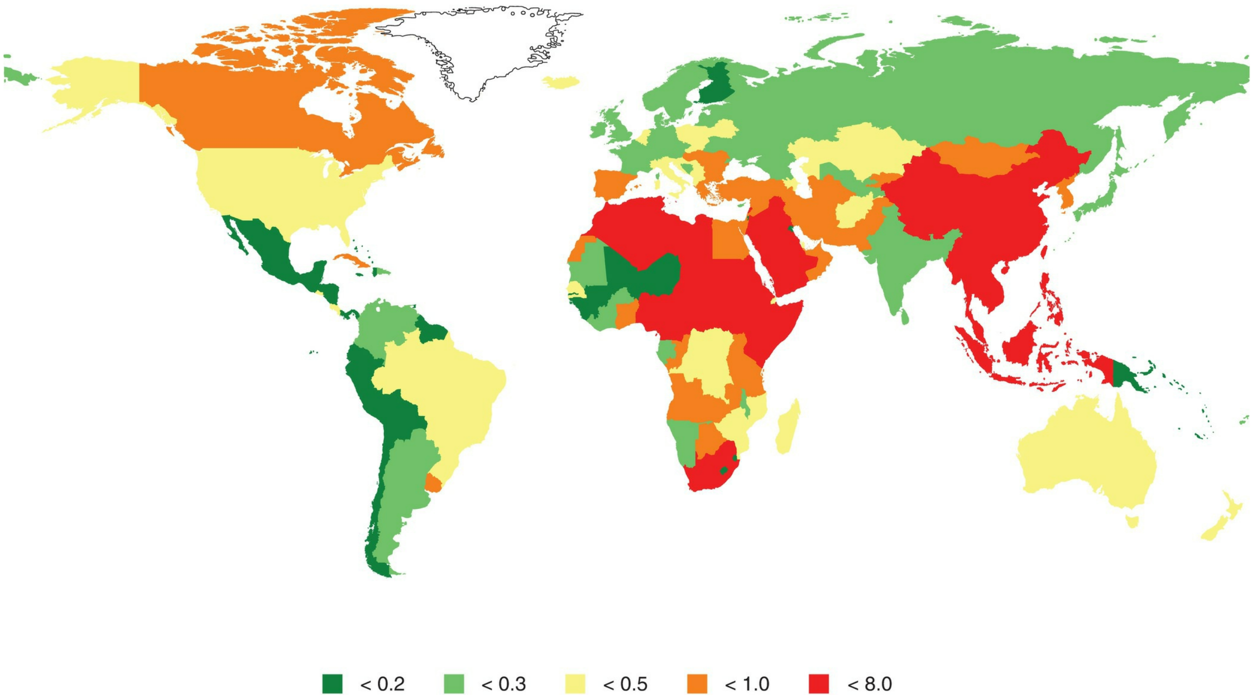

Figure 25.5. Nasopharyngeal carcinoma: Estimated age-standardized incidence rate/100,000; GLOBOCAN 2008 (IARC).
(From GLOBOCAN 2008: International Agency for Research on Cancer (IARC), 2013.)

Human immunodeficiency virus (HIV) is associated with malignancies of the head and neck. The prevalence of HIV is highest in developing countries; two-thirds of HIV-positive people live in sub-Saharan Africa and the prevalence of HIV in South Africa is 18%.[6] Engsing et al.[7] reported in a Danish study that even though HIV status was associated with a higher risk of developing squamous cell carcinoma of the head and neck, it appeared to be a marker of family-related risk factors associated with head and neck carcinoma rather than immunosuppression or HIV infection causing carcinoma per se. HIV is associated with Kaposi sarcoma and non-Hodgkin (and Hodgkin) lymphoma. In a study of a cancer population, those with squamous cell carcinoma of the conjunctiva were 10 times more likely to be HIV positive than those with other cancers.[8]

Although the association of HPV infection with squamous cell carcinoma of the oropharynx is now well established, few studies exist of HPV and cancer of the oropharynx in developing countries.

IMPORTANT CONSIDERATIONS WHEN TREATING HEAD AND NECK CANCER IN DEVELOPING COUNTRIES

It is generally not possible to simply apply treatment protocols suited to developed world centers of excellence to head and neck patients in a developing world setting. Important considerations when making treatment decisions are next discussed.

Advanced Cancer

Patients in developing countries are more likely to present with advanced cancer[9,10]; consequently, treatment is primarily palliative.[11] Onyango[9] reported that 58% of laryngeal cancer patients required emergency tracheostomy in Kenya. Even South Africa, a middle-income country, 52% of patients undergoing total laryngectomy in Cape Town required emergency tracheostomy.[12] Late presentation may be attributed to ignorance, poverty, poor access to specialized health services, and patients turning initially to traditional healers and traditional remedies.

The adverse consequences of delayed presentation are compounded by long waiting lists for surgery and irradiation. Frequently, patients become inoperable while awaiting surgery or radiation therapy; this complicates initial patient selection and treatment planning. In a study of patients awaiting treatment for head and neck cancer, Jensen et al.[13] reported that 1 month's delay was associated with 62% increase in tumor size and 20% in new nodal metastases and that cancers were upstaged (TNM) in 16% of patients studied; mean tumor volume doubling time was 3 months. Some institutions administer "holding chemotherapy" (methotrexate or platinum-based drugs) to slow tumor progression while patients await definitive treatment, even though there is no published evidence that this practice improves the outcome.

HIV Status

When managing HIV-positive patients with squamous cell carcinoma of the head and neck, especially when resources are limited, an oncology team may

need to consider the following:

- *Is radiotherapy in HIV-positive patients accompanied by the potential for increased mucosal and cutaneous toxicity?* Although many reports exist of radiotherapy-induced skin and mucosal toxicity with Kaposi sarcoma, the few reports of toxicity with other head and neck malignancies indicate good tolerance to radiation ± chemotherapy.[14–16]
- *Should antiretroviral therapy be initiated in immunocompromised patients to boost CD4 counts prior to initiating (chemo)radiation therapy?* Radiation therapy can suppress CD4 counts; therefore, even though it may seem reasonable to commence antiretroviral therapy to boost depressed CD4 counts prior to initiating radiation, there are no controlled studies to address this. Although interactions between antiretroviral therapy and radiation have not been well documented in the literature, there is a theoretical concern about the additive myelosuppressive effects of certain antiretroviral agents and myelosuppressive chemotherapeutic agents used with head and neck cancers, for example, platinum alkylators such as cisplatin and carboplatin.[16]
- *What is the anticipated life expectancy of an HIV-positive patient?* Adults that commence antiretroviral therapy before CD4 counts drop to <200 cells/mm3 have about 80% of normal life expectancy; even the most severely ill HIV patients treated with antiretroviral therapy have at least an 80% chance of surviving 2 years.[17]
- *How do CD4 count and HIV status affect surgery?* Even major surgery does not depress CD4 counts,[18] and HIV status per se does not affect the incidence of early surgical complications.[19] A low CD4 count (<100 cells/mm3) has however been reported to be a predictor of postoperative sepsis.[20,21] Instituting antiretroviral therapy prior to surgery has the benefits of reducing viral load (viral exposure to the surgical team) and increases patients' CD4 counts.

In view of the above, there is inadequate evidence to modify treatment in generally healthy HIV-positive patients (CD4 count >350 cells/mm3) with head and neck cancer.[16] There is also little reason to routinely determine the HIV status of an otherwise healthy-looking head and neck cancer patient from an oncologic perspective alone; only when HIV infection causes general

ill health and immunosuppression may HIV status preclude patients from undergoing major surgery or chemoradiation.

Patient Prioritization

Deciding who or who not to treat when the burden of head and neck cancer exceeds available treatment resources is perhaps the most difficult task oncologists and surgeons in developing countries have to face. It involves ethical and practical considerations such as tumor stage, prognosis, palliation versus cure, comorbidities, nutritional status, age, socioeconomic status, social support structure, distance from the closest treatment center, likelihood of regular follow-up, parental status, employment, and the ethical dilemma of whether to deny publicly funded treatment to patients originating from a foreign country without adequate treatment facilities. As access to surgery and radiotherapy are the principal bottlenecks in many developing countries, it is reasonable to prioritize patients with the most curable (early-stage) malignancies, especially when adjuvant radiation is not available or will be significantly delayed following resection of advanced malignancies.

TREATMENT MODALITIES

Surgery

Surgery is often the principal or only treatment available to a patient with cancer of the head and neck in developing countries. Yet, surgeons lack head and neck surgical training in many developing countries, and modern surgical technology (bipolar cautery, laser, transoral robotic surgery, endoscopic surgery), frozen section, blood products, adequate operating time, good anesthesia, and intensive care support are often lacking.[22] Surgeons in developing countries need to keep abreast of and adapt modern surgical principles and techniques to a lower technology practice, for example, substitute transoral microsurgery for early laryngeal cancer with laryngofissure and other open partial laryngectomy procedures, ensure wider tumor resection margins in the absence of frozen section control and postoperative radiation therapy, liberally employ elective neck dissection in the absence of sophisticated imaging, and rely on a range of pedicled rather than microvascular free tissue transfer flaps to reconstruct surgical defects.

Radiotherapy

Radiotherapy is central to the treatment of head and neck cancer but is unavailable in much of the developing world. Abdel-Wahab et al.[11] reported that only 23/52 African countries had radiotherapy facilities and that facilities were concentrated in the southern and northern parts of the continent (**Fig. 25.6**), that brachytherapy resources were available in only 20 countries, and that because only 2% of African countries have modern imaging equipment, treatment planning systems and curative treatment is generally based on two-dimensional imaging and treatment planning. Tatsuzaki and Levin[23] reported significant unavailability of radiation facilities in Asia and the Pacific regions[23]; and Zubizarreta et al.[24] reported a major restriction to access to radiotherapy services in 16/18 South American countries due to insufficient numbers of specialists.[24]

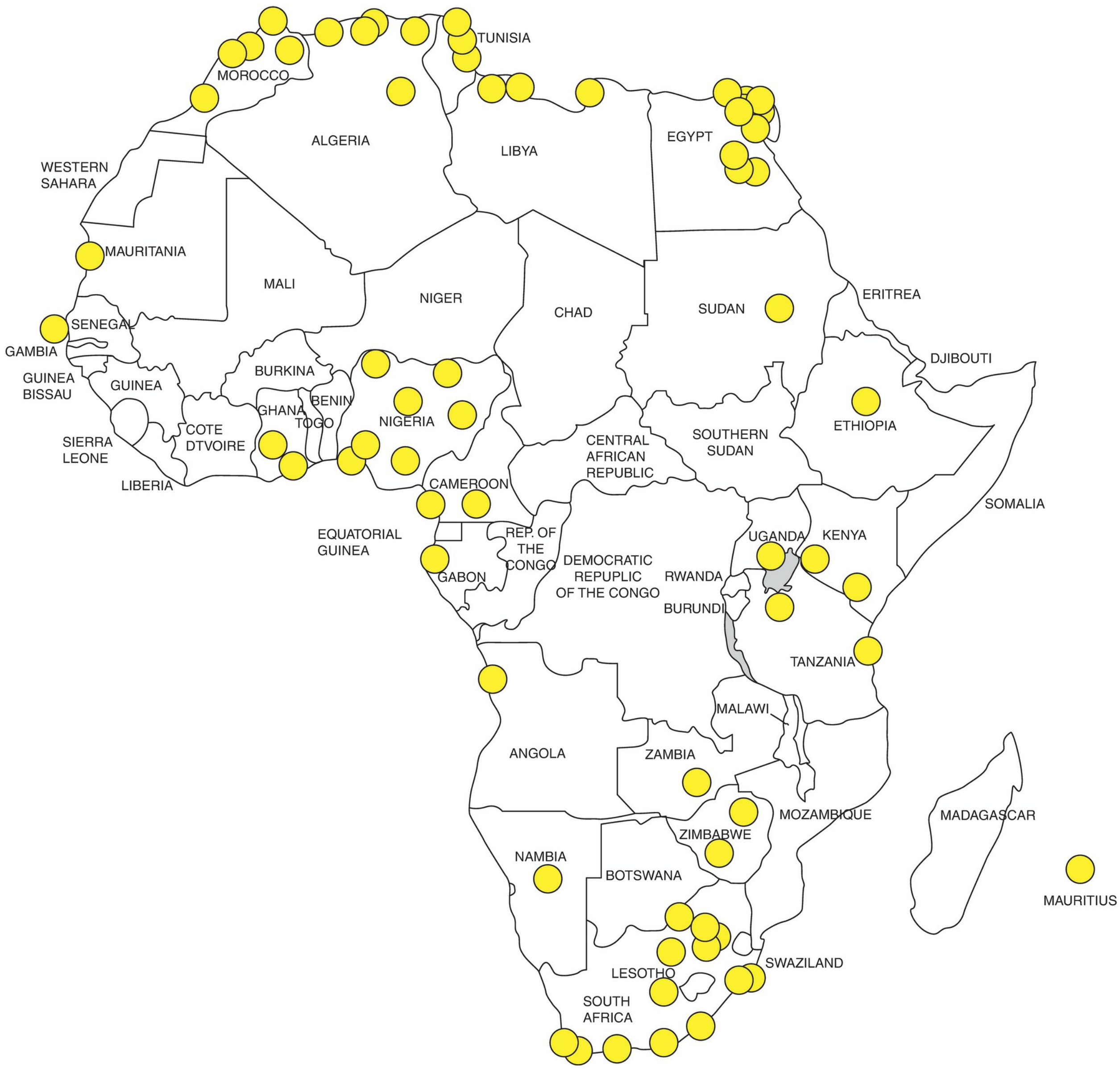

Figure 25.6. Radiation therapy services in Africa. (From Abdel-Wahab M, Bourque J-M, Pynda Y, et al. Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. *Lancet Oncol.* 2013;14(4):e168–e175.)

Therefore, most radiation services in Africa and elsewhere in the developing world are fairly basic and deliver mainly palliative care.[11] Radiation therapists in such centers need to be cautious about extrapolating favorable results emanating from modern radiation therapy centers of excellence to situations where reliance is placed on older technology. Patients that undergo radiation to the head and neck require long-term follow-up to

detect and manage delayed radiotherapy-related morbidity. For example, because hypothyroidism increases over time and is present in 25% of patients at 5 years, patients require long-term monitoring of thyroid function.[25] Yet as many patients in developing countries do not return for regular follow-up, the ability to monitor thyroid function and treat hypothyroidism has to be considered when selecting patients for radiation to the head and neck.

Chemoradiation

Concurrent chemoradiation (CCRT) is widely employed for organ sparing in patients with squamous cell carcinoma of the oro-, hypo-, and nasopharynx and larynx in developed countries. It also has an 8% advantage in terms of locoregional control (LRC) and survival rates compared to radiotherapy alone.[26] However, to achieve such favorable outcomes, the "package of care" must include sophisticated imaging (CT, MRI, PET) for both treatment planning and follow-up, medical and intensive care support for chemotoxicity, short- and long-term PEG feeding, complex salvage surgery for persistent cancer or disease recurrence, as well as dental, speech, swallowing, and audiologic rehabilitation facilities. Salvage surgery requires high levels of surgical expertise that include proficiency with free tissue transfer flaps.

Because chemoradiation is an expensive, toxic,[26] and complex treatment and requires a "package of care" not available in many developing world centers, it has to be employed with great circumspection in a developing world setting. Kumar et al.[27] reported a 14% mortality rate during and within 30 days of treatment in patients with advanced head and neck cancer treated with concomitant boost radiotherapy with concurrent weekly cisplatin at a tertiary hospital in India; the authors attribute this high mortality to poor support to deal with acute morbidity, poverty, malnutrition, illiteracy, and poor hygiene and conclude that "on present evidence in the setting of a developing country, CCRT with concurrent cisplatin cannot be recommended as primary therapy in advanced head and neck cancers without formal comparison with other treatment modalities" (**Fig. 25.7**). Therefore, if chemoradiation is to be considered, patients must be carefully selected to predict favorable functional outcomes by considering factors such as age, general health, social support, immune (HIV) status, and tuberculosis, and the "package of care" mentioned above should be available.

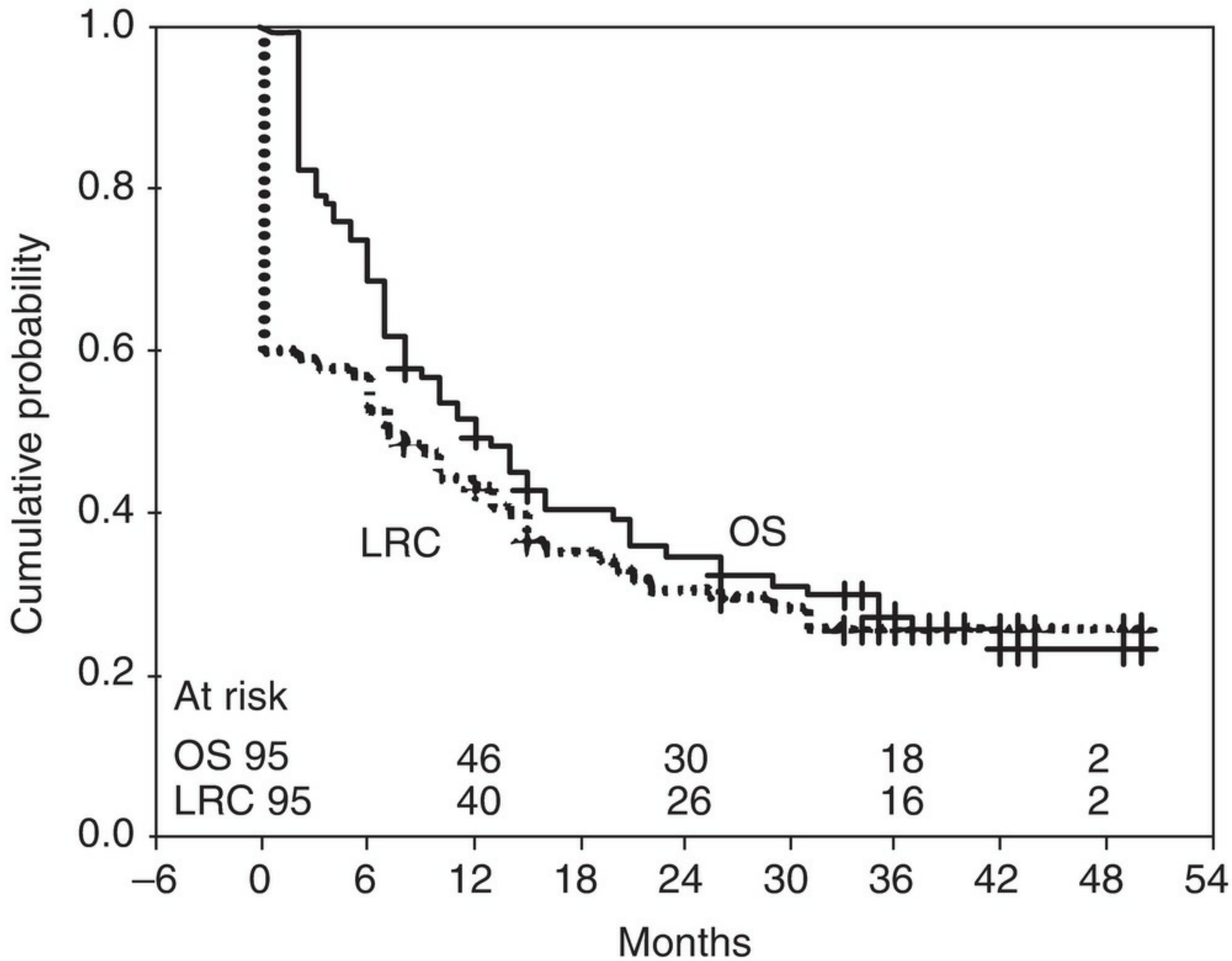

Figure 25.7. LRC and overall survival (OS). (From Kumar S, Pandey M, Lal P, et al. Concomitant boost radiotherapy with concurrent weekly cisplatin in advanced head and neck cancers: a phase II trial. *Radiother Oncol.* 2005;75(2):186–192.)

Altered Fractionation

A variety of altered fractionation schedules, including hyperfractionation, accelerated radiotherapy, or a combination of the two, provide improved local control and survival compared with conventional radiotherapy. *Accelerated radiotherapy* is perhaps better suited to a developing world setting than chemoradiation as it is cheaper and better tolerated. Overgaard et al.[28] reported in a multicenter study of squamous cell carcinoma of the larynx, pharynx, and oral cavity that a six-fraction-per-week radiation schedule resulted in significantly improved LRC at 5 years compared to conventional schedules of five treatments per week. Despite increased acute morbidity,

accelerated radiotherapy did not cause increased late morbidity and had the benefit of reducing overall treatment by 1 week. *Concomitant boost radiotherapy* with a second daily fraction to the gross tumor volume in the final 10 to 12 days of treatment also reduces the overall treatment time, thus reducing the chance of repopulation and improving local control.[29] However, both these schedules would require some reorganization to accommodate the second daily fraction unless in the former case, a radiation therapy department already treats patients 6 days per week.

MANAGEMENT ALGORITHMS

Selecting appropriate management algorithms for head and neck cancer patients in developing countries is particularly challenging and involves making complex, individualized decisions generally without the benefit of special investigations such as FNAC, CT, MRI, PET–CT, and HPV status. Unlike the situation in well-resourced health systems, it may not always be possible for treatment to be protocol driven as the majority of patients are dependent on state run medical services characterized by inadequate health infrastructure and resources. For the same reasons, management algorithms designed for developed world settings are not always relevant, for example, because tuberculosis mimics metastases on PET scan, its utility as a staging tool is limited in societies where tuberculosis is endemic. Reliance therefore frequently has to be placed on clinical acumen, experience, intuition, and institutional bias, often in the absence of scientific evidence to support clinical decisions. Investigations and treatment have to be tailored to the individual patient taking into account resource constraints, for example, availability of CT, MRI, operating rooms, ICU, radiation facilities, and blood transfusions; treatment delays (often many months); likelihood of regular follow-up; access to drugs, for example, thyroid and calcium replacement; nutritional status; social support; poverty; comorbidities (often poorly treated or neglected) including HIV; cultural bias; and the availability of surgical expertise, radiation therapy, and chemotherapy. Certain principles will now be touched on that may be considered when designing management algorithms in resource-constrained settings.

History

Be cognizant of cultural and religious values of patients as this may affect how one manages cancers of the head and neck. Inquire about risk factors including betel nut, areca nut, reverse smoking, chewing tobacco, and comorbidities, for example, tuberculosis.

Metastatic Workup

When access to operating time and adjuvant radiotherapy is limited, one could argue for employing CT scan (even if it is a limited and expensive resource) to rule out pulmonary metastases before inappropriately committing scarce surgical resources to more advanced T and N stage cancers that have metastases not evident on CXR.

N0 Neck

It is reasonable to advocate a lower threshold to electively treat the N_0 neck with selective neck dissection in cases of unreliable follow-up; lack of imaging, for example, ultrasound, CT, or MRI, both initially and at follow-up; and lack of timely adjuvant radiation. In the absence of frozen section, surgeons should have a low threshold to convert a selective to a modified neck dissection when enlarged lymph nodes are encountered, especially in the absence of postoperative irradiation facilities.

N+ Neck

Even though lymphadenopathy in patients from poorer communities may be a result of untreated dental and pharyngeal infections, HIV, or tuberculosis, palpable nodes within the lymphatic drainage area of a primary cancer should be treated with modified or radical neck dissection to avoid undertreating a neck that harbors metastases. Even though the presence of ≥2 cervical nodal metastases is generally considered to be an indication for adjuvant radiation, the evidence to support this threshold is tenuous; hence, centers that lack capacity to provide postoperative radiation to all deserving patients could argue that this threshold for adjuvant radiation be adjusted upward so that patients most likely to benefit, for example, with positive margins, extracapsular spread, and large tumor volumes are not deprived of adjuvant radiation.[30]

Reconstruction

Excellent functional results with microvascular free tissue transfer flaps can be achieved in a developing world setting[31]; however, such surgery is time consuming and requires specialized training. In the absence of reconstructive expertise with microvascular free tissue transfer flaps, surgeons should become proficient at using a range of pedicled flaps, for example, buccinator, buccal fat pad, temporalis, nasolabial, pectoralis major, forehead, deltopectoral, and latissimus dorsi flaps.

Oral Cavity

When postoperative radiation is unavailable, surgery for T1 and T2 cancers should be prioritized, including cancers that are staged T4 due to limited bony invasion that can be resected by marginal or segmental mandibulectomy or partial maxillectomy. Cancers of the tongue and floor of mouth that are digitally palpable (likely to be >4 mm thick) or are staged ≥T2 should undergo elective neck dissection due to the significant likelihood of occult cervical metastases. Preserving oral function is crucial; other than microvascular free tissue transfer flaps, surgeons can use pedicled flaps, for example, buccinator, buccal fat pad, temporalis, nasolabial, and pectoralis major flaps; with inferior or total maxillectomy, one must separate the oral cavity from the nose; if prosthetic expertise is not available, this can be achieved with temporalis muscle flaps. Without the facility to reconstruct bone (e.g., free fibula flap), mandibular resection should not be extended beyond the midline to avoid the crippling and unsightly *Andy Gump* deformity.

Oropharynx

Management of cancers of the oropharynx has undergone a paradigm shift in recent years following the realization that HPV infection is both an etiologic and prognostic factor for a subset of oropharyngeal squamous cell carcinomas, the introduction of transoral robotic surgery to resect oropharyngeal tumors, as well as attempts to reduce the morbidity of chemoradiation by accepting smaller resection margins when combined with postoperative radiation. However, HPV testing, transoral robotic surgery, and chemoradiation are generally not available in developing world centers;

neither is the ability to deal with adverse consequences of chemoradiation. Surgery and radiation therefore remain the mainstay of treatment. Pedicled flaps used to reconstruct soft palate, lateral pharyngeal wall, or base of tongue may include buccinator, buccal fat pad, temporalis, and pectoralis major flaps.

Larynx and Hypopharynx

Early cancers are commonly excised with CO_2 laser in developed world centers. Advanced cancers (dysfunctional larynx, cartilage invasion, tracheostomy for stridor) are treated with total laryngectomy. The remainder are offered chemoradiation with surgery reserved for salvage. However, CO_2 laser is generally not available in developing world centers; chemoradiation is expensive and the package of care required to manage both acute and late consequences and complications of chemoradiation (dysphagia, PEG feeds, cancer surveillance with MRI and PET scans, complex salvage surgery, hypothyroidism, hypocalcemia) is lacking. Therefore, such centers have to rely on open approaches such as laryngofissure; vertical partial, supraglottic, supracricoid, and near-total laryngectomy for smaller cancers; and total laryngectomy for advanced cancers. When performing a total laryngectomy, the surgeon should attempt to preserve both thyroid lobes and the parathyroids to minimize the risks of hypothyroidism and hypoparathyroidism, particularly in settings where thyroid and calcium replacement and monitoring are difficult or unavailable. With a dedicated speech therapy service, postlaryngectomy tracheoesophageal fistula speech results can be achieved that match those of developed world centers even in poor, illiterate patients living long distances from treatment centers.[32] Voice prostheses are however expensive; this has led to strategies such as using removable prostheses as indwelling prostheses to reduce expense.[32] HME devices are unaffordable in developing countries; yet cheap, homemade cloth stoma covers (bibs) are as effective for maintaining the tracheal climate.[32] Although esophageal speech is inexpensive, only 27% of patients in a Brazilian study mastered esophageal speech.[33] Another option is to use mucosal shunts; however, the surgery is technically difficult and can be used only in highly selected patients with good pulmonary function who can cope with aspiration.[33] Because of a severe shortage of speech therapists in many developing world countries,[22,33] an electrolarynx is a reasonable alternative

to achieve postlaryngectomy speech.

Nasopharynx

Cancers of the nasopharynx are principally a developing world problem (Fig. 25.5). Chemoradiation is the mainstay of treatment and the meta-analysis of chemotherapy in nasopharynx carcinoma (MAC-NPC) meta-analysis showed that the 5-year survival improved by 6%, from 56% to 62%, with the addition of concurrent chemotherapy to the radiotherapy.[34] However, the supportive care required for the extreme chemotoxicity is not always available in developing countries. Patients generally present with advanced disease; in an unpublished study conducted in Cape Town, South Africa, 50% of patients presented with stage 4B disease of which 28% did not complete treatment for socioeconomic reasons (Dalvie et al., unpublished data). Hence, it may be prudent to accept the lower survival rate with radiotherapy alone than try to improve it with CCRT with its attendant morbidity. Intensity-modulated radiotherapy (IMRT/complex 3-D conformal radiotherapy) increases local control by allowing dose escalation to the tumor and can improve the quality of life by reducing xerostomia.[4] Although it is now regarded as the standard of care for nasopharyngeal cancer, it is not generally available in developing countries.

Thyroid

Most thyroidectomies in developing countries are done by surgeons not specializing in endocrine surgery. Bilateral recurrent laryngeal nerve injury causing airway compromise or hypoparathyroidism causing hypocalcemia in situations where monitoring serum calcium and treating hypocalcemia with calcium and vitamin D are not possible may have fatal consequences. Regardless of surgical expertise, complication rates rise with the extent of resection. Subtotal thyroidectomy preserves the blood supply to the ipsilateral parathyroid glands and reduces the risk of hypocalcemia. Thyroid lobectomy almost never causes significant hypoparathyroidism. Total thyroidectomy is however associated with both increased short- and long-term morbidity relating to recurrent laryngeal nerve paralysis and hypocalcemia, particularly in an occasional thyroid surgeon’s hands. In the absence of convincing evidence that total thyroidectomy confers survival benefit for favorable, differentiated thyroid cancer[35,36] (especially when I131 therapy is not

available), coupled with the morbidity and mortality of total thyroidectomy in a setting where calcium monitoring and replacement are suboptimal, the occasional thyroid surgeon practicing in a developing world center may be wise to perform only thyroid lobectomy or subtotal thyroidectomy for favorable differentiated thyroid cancer.

OPPORTUNITIES TO IMPROVE HEAD AND NECK CANCER CARE IN DEVELOPING COUNTRIES

It should be apparent to clinicians, researchers, and health planners that the developing world presents great opportunities to make a substantial difference in terms of “lives saved” of head and neck cancer patients. The developing world does not have the human, infrastructural, or financial resources to address its enormous cancer burden without global assistance. A multifaceted approach is required including lobbying international organizations, governments, and aid organizations to support infrastructure development and research and for industry to provide appropriate and affordable technology. A global effort is required to educate and train oncologists and surgeons to manage head and neck cancer in developing countries.

Both developed and developing world clinicians and medical centers can contribute in many ways *inter alia:*

Prevention and Screening

Public awareness campaigns and educating primary health care workers about the risks of nicotine, alcohol, and HPV, as well as the need for albinos to avoid sun exposure, are required. Despite the survival benefit of earlier detection of cancer, a Cochrane review reported that visual screening for oral cancer did not have any survival benefit, although there was some evidence that it might be effective in high-risk patients.[37,38] Techniques using toluidine blue staining, brush biopsy or cytology, or fluorescence imaging as primary screening tool or as adjunct for screening have also not been shown to have any benefit.[35] Consequently, it would appear that, based on current evidence,

there are more important interventions that will improve head and neck cancer outcomes in a developing world setting than diverting scarce human and financial resources to screening.

Education and Training

Oncologists and surgeons need to be trained to manage head and neck cancer through residency programs, clinical fellowships, *in loco* training, and international support.

Educational Resources

Clinicians in developing countries often cannot access textbooks and journals, both of which are generally unaffordable. Hence, open access to journals, textbooks, and educational resources should be encouraged. Examples include the *HINARI Programme*, a collaboration between the WHO and major publishers to enable low- and middle-income countries to gain access to health literature (http://www.who.int/hinari/en/), textbooks such as the *Open Access Atlas of Otolaryngology, Head and Neck Operative Surgery* (http://www.entdev.uct.ac.za/guides), and a variety of open-access journals.

Outreach

Many outreach projects exist whereby clinicians visit and work in developing countries. However, for such outreach projects to be effective, they need to focus on developing sustainable head and neck cancer programs. This requires that outreach projects be integrated with existing local services and that the focus should be on the teaching and training of local clinicians and clinical teachers.

Research

Research should be encouraged in fields such as epidemiology, preventative strategies, and designing and validating resource-appropriate management algorithms for head and neck cancers in poorly resourced developing world contexts.

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26 Lymphomas Presenting in the Head and Neck: Current Issues in Diagnosis and Management

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Lymphoma is the fifth most common cancer in Western countries, with 80,000 new cases estimated in the United States in 2014.[1] Up to a quarter of extranodal lymphomas present in the head and neck, and 8% of supraclavicular node fine needle aspiration (FNA) are lymphoma.[2] The 2008 World Health Organization (WHO) classification recognizes 54 distinct subtypes of lymphoma, which can be broadly classified as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) with the latter category further divided according to their postulated normal cell of origin being of B- or T-cell lineage.[3] Although lymphoma typically presents with lymphadenopathy, extranodal involvement is common with the most frequently involved extranodal site in the head and neck area being the tonsil, followed by the nasopharynx, oral cavity, salivary glands, paranasal sinuses, and base of the tongue. HL rarely presents with extranodal disease; however, in NHL, extranodal sites of involvement may be the primary (or exclusive) disease manifestation. Lymphomas are typically both chemo- and radiosensitive tumors and may be cured in a significant proportion of patients, even when presenting with disseminated disease. Therefore, the distinction of lymphomas from carcinomas and other malignancies is critical. The purpose of this chapter is to review the clinical presentation, diagnosis, staging, and treatment of this group of diseases with emphasis on patient treatment when presentation includes localized nodal or extranodal disease in the head and neck region.

CLINICAL PRESENTATION

The clinical presentation of lymphoma varies considerably depending on the anatomic site and underlying subtype; however, painless nodal enlargement is typical. Aggressive lymphomas with rapid proliferation may result in painful nodes due to central necrosis. Constitutional or “B” symptoms (unintentional weight loss, night sweats, unexplained fevers) are usually associated with aggressive lymphomas with advanced stage and are uncommon in patients with indolent or localized disease. An overview of typical presentations of lymphomas in the head and neck is presented in **Table 26.1**. In addition to standard evaluation for other lymphadenopathy and enlargement of the liver and spleen, physical examination should also specifically focus on evidence of superior vena cava obstruction, which may indicate a large mediastinal mass.

Table 26.1 Anatomic Sites, Common Histologic Subtypes, and Clinical Manifestations of Lymphoma of the Head and Neck

Anatomic Location	Common Histologic Subtypes	Clinical Presentation
Cervical and supraclavicular nodes	Hodgkin lymphoma Diffuse large B-cell lymphoma Follicular lymphoma	With a rubbery/nodal enlargement Alcohol-induced node pain (<5% HL only)
Tonsils	Diffuse large B-cell lymphoma Follicular lymphoma Lymphoplasmacytic lymphoma Mantle cell lymphoma	Fleshy, nonulcerated unilateral tonsillar mass, odynophagia, globus sensation, dysphagia, and hearing loss secondary to otitis media
Salivary glands	Marginal zone lymphoma	Asymmetric swelling
Nasopharynx and paranasal sinuses	Extranodal NK-cell lymphoma Diffuse large B-cell lymphoma	Nasal obstruction, epistaxis, sinusitis, bloody drainage, or pain
Orbits, ocular adnexal tissue	Extranodal marginal zone lymphoma Diffuse large B-cell lymphoma	Facial swelling, ocular discomfort, diplopia, proptosis, conjunctival lesions, lacrimal duct blockage
Thyroid	Diffuse large B-cell lymphoma Marginal zone lymphoma	Swelling of the neck, dysphagia, dysphonia or hoarseness, or facial edema
Base of the skull, leptomeninges, brain	Diffuse large B-cell lymphoma Mantle cell lymphoma Burkitt lymphoma Lymphoblastic lymphoma Double-hit lymphomas Intravascular large B-cell lymphoma	Cranial nerve palsies, headache, pyramidal weakness, dysphasia, ataxia, vertigo

CLASSIFICATION

The classification of lymphoid neoplasms has evolved over time from a morphologic classification system (Rappaport, Kiel) into the current WHO classification, which incorporates molecular, immunophenotypic,

cytogenetic, morphologic, and clinical features.[3] Lymphomas can broadly be classified according to their normal hematopoietic counterpart (B-cell malignancies, T- and NK-cell malignancies, or HL) and the point of maturation of the cells (precursor or mature). Generally speaking, there is an inverse correlation between degree of maturation and proliferation rate. For example, the most immature (lymphoblastic lymphoma) is considered a nodal variant of acute lymphoblastic leukemia and is rapidly fatal if untreated. At the other end of the spectrum, indolent subtypes such as follicular lymphoma (FL) may sometimes be observed safely without treatment for more than 10 years. It is important to note that even within histologic subtypes, there exists considerable heterogeneity in disease biology, clinical behavior, and outcome. **Tables 26.2** and **26.3** list the current (2008) WHO classification of B-cell and T- and NK-cell lymphomas, respectively.

Table 26.2 WHO Classification of Mature B-Cell Lymphomas

Mature B-Cell Lymphomas

Diffuse large B-cell lymphoma (DLBCL), not otherwise specified

- T-cell/histiocyte-rich large B-cell lymphoma
- DLBCL associated with chronic inflammation
- EBV + DLBCL of the elderly
- Primary mediastinal B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary cutaneous DLBCL, leg type
- ALK+ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease

Follicular lymphoma

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Chronic lymphocytic leukemia/small lymphocytic lymphoma

- Splenic marginal zone lymphoma
- Lymphoplasmacytic lymphoma
- Nodal marginal zone B-cell lymphoma (MZL)
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- Lymphomatoid granulomatosis
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL

Hodgkin Lymphoma

Nodular lymphocyte-predominant HL

Classical HL

- Nodular sclerosis classical HL
- Lymphocyte-rich classical HL
- Mixed cellularity classical HL
- Lymphocyte-depleted classical HL

Bold text denotes entities commonly presenting in the head and neck.

Table 26.3 WHO Classification of Mature T- and NK-Cell Neoplasms

Mature T- and NK-Cell Lymphomas
Extranodal NK-/T-cell lymphoma, nasal type
Anaplastic large cell lymphoma (ALCL), ALK+
Anaplastic large cell lymphoma (ALCL), ALK–
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Systemic EBV$^+$ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis–like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorder
Lymphomatoid papulosis Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous aggressive epidermotropic CD8$^+$ cytotoxic T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous small/medium CD4$^+$ T-cell lymphoma

Bold text denotes entities commonly presenting in the head and neck.

ETIOLOGY

For any given individual patient with lymphoma, the precise etiology is usually unknown. However, risk factors for developing lymphoma have been identified. There is evidence for genetic susceptibility in lymphoma. Siblings of younger patients (<40) with HL have a 7-fold increased risk, and identical twins have a 100-fold risk.[4–6] Relatives of patients with NHL also appear to be at 4- to 10-fold increased risk of developing NHL.[5] Exposure to various substances including phenytoin, phenoxy herbicides (Agent Orange), hair dyes, dioxin, and benzenes has been found to have some correlation with an increased incidence of lymphoma.[7–10] Occupations in which exposure to these agents may occur are associated with a higher-than-normal risk for lymphoma; these include woodworking industries, agriculture, rubber and petrochemical industries, and dry-cleaning occupations. In contrast, exposure to ultraviolet sunlight (but not dietary vitamin D intake) and diets rich in fruits and vegetables have found to be associated with a reduction in the risk of developing lymphoma.[11–13] Exposure to prior radiation is also associated with increased risks of lymphoma, although the risk appears to be mainly in men.[14]

In addition to environmental factors, a variety of infectious agents have been associated with lymphomagenesis. In particular, chronic antigenic stimulation is thought to play an important role in the pathogenesis of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).[15] Of particular relevance to the head and neck setting, *Chlamydophila psittaci* DNA has been found in 47% to 80% of patients with ocular adnexal MALT lymphoma,[15] and eradication with doxycycline has been shown to be effective in some patients.[16] Other infectious agents associated with MALT lymphoma include hepatitis C (splenic), *Helicobacter pylori* (gastric), and *Borrelia burgdorferi* (cutaneous). Patients with chronic hepatitis B also appear to carry an approximately threefold increased risk of development of NHL.[17] Other viruses associated with lymphoma include human T-cell leukemia/lymphoma virus (HTLV)-1, Epstein-Barr virus (EBV), human herpes virus (HHV) 8, and HIV.[18,19] Immunosuppression, whether acquired (HIV infection, 11-fold),[20] congenital (combined variable immunodeficiency, 12-fold),[21] or iatrogenic (organ transplant recipients, up to 240-fold),[22] is probably among the most potent risk factors for the

development of lymphoma. Finally, other disorders characterized by dysregulation of the immune system have been associated with development of lymphoma. An increased incidence of NHL has been noted in patients with rheumatoid arthritis, celiac disease, Sjögren syndrome, dermatitis herpetiformis, inflammatory bowel disease, and acquired angioedema.[23,24] Lymphoma of the thyroid has been associated with either antecedent diagnosis or concomitant histologic finding of Hashimoto thyroiditis in more than 90% of cases, although <1% of patients with Hashimoto thyroiditis will develop lymphoma.[25]

EPIDEMIOLOGY

The incidence of lymphoma has been increasing, and lymphomas account for 3% to 4% of cancers worldwide.[26] Lymphoma is the leading cause of cancer death in adolescents and young adults.[1] HL has a bimodal incidence curve, the first peak occurring in teenagers to young adults and the second peak in older adults (>55 years).[27] There is a higher frequency among males than females. The incidence of NHL varies by histologic subtype: highly aggressive histologic subtypes (e.g., lymphoblastic and Burkitt lymphoma) are more common in children and adolescents, but most other forms of NHL are diseases of older adults, in particular, elderly adults (>60 years). NHL is more common in men than women, though the size of the discrepancy varies between subtypes.[3] HL accounts for around 10% of lymphoma diagnoses; in developed countries, 70% are nodular sclerosing, 20% are mixed cellularity, 5% are lymphocyte rich, and 1% are lymphocyte depleted, a group of diseases known collectively as classical HL, and 5% are nodular lymphocyte predominant, a disease that has a morphologic appearance that is distinct from the classical variants.[3] Among NHL, B-cell lymphomas are vastly more common and constitute 85% to 90% of NHL with T- and NK-cell lymphoma constituting the remainder.[3]

DIAGNOSTIC EVALUATION

Fine Needle Aspiration

When a patient presents with lymphadenopathy in the head and neck region,

FNA is helpful only as a minimally invasive test that can distinguish carcinoma or some other malignant process from lymphoma. If a diagnosis of lymphoma is favored by FNA findings, either excisional biopsy or image-guided core biopsy (if excisional biopsy is considered unfeasible) is needed, as the classification of lymphomas relies heavily on the histologic pattern of the malignancy in the lymph node. FNA may also result in both false negatives (e.g., concurrent reactive hyperplasia may occur as a response to the lymphoma in the lymph node) and false positives (e.g., infectious mononucleosis in which individual cells may appear aberrant). Therefore, a patient with a negative FNA but a clinically enlarging lymph node should undergo definitive excisional biopsy before a final diagnosis can be verified.

Biopsy

Biopsy of a representative lymph node is still the optimal procedure for establishing the diagnosis and subclassification of lymphomas. The selection of node for biopsy depends on the safety and accessibility of lymph nodes and the availability of baseline PET–CT imaging. The latter is valuable as the standardized uptake value (SUV) has some correlation with proliferation index in NHL,[28,29] and thus, the targeted biopsy of a node with SUV significantly higher than other involved nodal areas can be used to establish the presence of histologic transformation of an indolent lymphoma.[30] A prospective study of 38 patients with indolent lymphoma undergoing PET-CT–directed biopsy used ROC analysis to identify an optimum SUV cutoff of 14, which resulted in a positive predictive value of 93.9% and specificity and negative predictive value of 95.3% for detecting histologic transformation.[31] As the presence of histologic transformation may have significant treatment and prognostic implications, in cases where there is heterogeneous nodal ^{18}F-flurodeoxyglucose (FDG) avidity present, the area with highest SUV should be biopsied if feasible. Excisional biopsy is preferred; however, in cases where excisional biopsy is not feasible, CT-guided core biopsy is an acceptable alternative. Rebiopsy is usually necessary in patients who have residual FDG-avid masses at the completion of therapy, particularly if escalation of therapy is planned as the finding of nonmalignant pathologies, such as necrosis, foamy macrophages, or sarcoidosis, is not unusual in this setting.[32,33] Rebiopsy is also needed at time of relapse as it is possible for indolent lymphomas to undergo transformation to aggressive lymphomas

such as diffuse large B-cell lymphoma (DLBCL) and vice versa.[34,35] The entire lymph node should be removed in one piece and its capsule maintained intact. The lymph node must be handled gently during surgery to minimize crush artifact, and the tissue should be placed fresh in saline and transported to the laboratory immediately to minimize deterioration of the sample. Biopsies of the tonsil, base of the tongue, and nasopharynx are done in the same manner as biopsy in diagnosis of squamous cell carcinoma.

Pathologic Studies

Histology

Histologic evaluation of a lymph node involved by lymphoma should include an assessment of tumor cell morphology, growth pattern of the lymphoma (diffuse or follicular), and the presence of composite lymphomas (where two histologically distinct lymphomas exist in a single lymph node or in different nodes contemporaneously in the same patient). Immunohistochemistry can confirm hematopoietic origin of the tumor (CD45 or LCA), distinguish tumor cells from normal or reactive lymphoid tissue, determine B-cell (CD20, PAX5) or T-cell (CD3, CD5) lineage and proliferation index (Ki 67), assist in the determination of specific subtype (e.g., cyclin D1 expression in mantle cell lymphoma or CD10, BCL6, and MUM1 to determine cell of origin in DLBCL),[36] and give prognostic information (coexpression of MYC and BCL2 or BCL6 in the highly aggressive double-hit lymphoma).[37] Additional surface marker studies such as keratin, mucin stain, or S100 may also be useful in excluding squamous cell carcinoma, adenocarcinoma, and melanoma, respectively.

Flow Cytometry

Flow cytometric analysis is a useful complementary tool in the diagnosis of lymphomas as it allows for the detection of two or more markers simultaneously (e.g., concurrent expression of CD19 and CD5 in small lymphocytic and mantle cell lymphoma), has rapid turnaround, and can provide a more quantitative assessment of the intensity of antigen expression than immunohistochemistry. However, it gives no information about cellular morphology and is not useful in the diagnosis of HL as the neoplastic Reed-

Sternberg cells constitute <1% of the cellular population in involved lymph nodes. In the setting of NHL, when performed on FNA specimens, it can distinguish B-cell or T-cell lineage, although in most cases accurate subtyping is still contingent on evaluation of an adequate biopsy sample. It is also more sensitive than cytology alone in detecting lymphoma cells in cerebrospinal fluid (CSF) in patients with leptomeningeal disease and should always be requested in addition whenever lumbar puncture is performed.[38–40]

Cytogenetic Analysis

Cytogenetic analysis by conventional karyotype or fluorescence in situ hybridization (FISH) may be required in specific lymphoma subtypes or clinical presentations. These studies can be performed on both fresh and formalin-fixed paraffin-embedded tissue and will usually be requested as needed by the reporting pathologist or treating hemato-oncologist. FISH can identify a range of chromosomal abnormalities including deletions, gains, translocations, and duplications and can be used to provide both diagnostic and prognostic information. **Table 26.4** summarizes clinically relevant chromosomal abnormalities in lymphoma.

Table 26.4 Important Chromosomal Translocations in Lymphoma

Histologic Subtype	Gene	Cytogenetic Abnormalities	Utility
Diffuse large B-cell lymphoma	*MYC*	MYC/8q24	*MYC* and *BCL2* and/or *BCL6* = double- or triple-hit lymphoma, adverse prognosis
	BCL2	BCL2/18q21	
	BCL6	BCL6/3q27	
Burkitt lymphoma	*MYC-IGH*	t(8;14) (q24q32)	Diagnosis
	MYC-IGK	t(2;8)(p12q24)	
	MYC-IGL	t(8;22)(q24q11)	
Follicular lymphomas; some large-cell lymphomas	*IGH-BCL2*	t(14;18) (q32q21)	Diagnosis
Mantle cell lymphoma	*CCND1-IGH*	t(11;14) (q13q32)	Diagnosis
Marginal zone lymphomas	*FOXP1-IGH*	t(1;14) (p22q32)	BIRC3-MALT resistant to antibiotic therapy
	IGH-MALT1	t(3;14)(p14.1q32)	
	BIRC3-MALT1	t(11;18)(q12q21)	
Anaplastic large-cell lymphoma, ALK+	*NPM1-ALK*	t(2;5) (p23q35)	Diagnosis, prognosis (ALK+ better than ALK−)
Extranodal NK-cell lymphoma, nasal type		del(6)(q21q25)	Uncertain

Molecular Analysis

In some cases, the distinction of malignant lymphoma from a reactive

lymphoid proliferation can be difficult, and molecular analysis for polymerase chain reaction for immunoglobulin gene rearrangements (in B-cell NHL) or T-cell receptor gene rearrangements (in T-cell NHL) to demonstrate clonality can be helpful in some cases.[41] Perhaps the defining milestone in medicine in the last decade has been the advent of high-throughput whole-exome sequencing. The increasing availability and decreasing cost of this technology have resulted in definition of the mutational landscape of many lymphoma subtypes.[42–45] These advances will fundamentally change the way lymphomas (and for that matter, all cancers) are classified, diagnosed, and treated. However, at the present time, technologies such as next-generation sequencing, nanostring, and whole-exome sequencing remain largely research tools and are not widely available in diagnostic pathology laboratories.

Staging

For the last 40 years, the Ann Arbor classification system has remained the most widely used staging system for lymphomas (**Table 26.5**).[46] Originally designed for HL (which spreads in a pattern of anatomic contiguity), the system classifies patients as having limited (I/II) or advanced (III/IV) stage—a division that remains critically important for prognostic and therapeutic purposes for many (but not all) types of lymphoma. Although widely used in NHL, it is not ideally suited to describe disease extent due to frequent involvement of extranodal sites. Furthermore, in both HL and many subtypes of NHL, specific prognostic indices have been developed, which may incorporate stage as only one of several factors (**Table 26.6**).

Table 26.5 Ann Arbor Staging Classification

Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (II_E)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (III_E) or spleen (III_S) or both (III_{SE})
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement
A	Absence of B symptoms
B	Unexplained fever (>38°C), night sweats, unintentional weight loss >10% of body weight

From Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res.* 1971;31:1860–1861.

Table 26.6 Prognostic Scoring Systems in Selected Lymphoma Subtypes

Histologic Subtype	Prognostic Index	Components (Points)	Risk Groups	Outcome
Diffuse large B-cell lymphoma	NCCN-IPI[47]	Age, normalized serum LDH		5-y OS
		Involvement of marrow, GIT/liver, lung, or CNS, stage III/IV, ECOG ≥2	Low Low intermediate High intermediate High	96% 77% 56% 38%
Follicular lymphoma	FLIPI-2[48]	Age, elevated serum LDH, hemoglobin <12 g/dL, marrow involvement, longest diameter of largest involved node 6 cm	 Low Intermediate High	5-y PFS 80 51 19
Mantle cell lymphoma	MIPI[49]	Age, ECOG, normalized LDH, WBC	 Low Intermediate High	5-y OS 60 35 20
Classical Hodgkin lymphoma (stage III/IV only)	IPS[50]	Albumin <4 g/dL, hemoglobin <10.5 g/dL, male, age >45, stage IV, white-cell count >15 × 10⁹/L, lymphocyte <8% of total WBC	Number of factors 0 1 2 3 4 5+	5-y FFP 84% 77% 67% 60% 51% 42%
Nodular lymphocyte-predominant Hodgkin lymphoma	NLPHL score[51]	Variant histology, albumin, gender	 Low Intermediate High	5-y PFS 95% 87% 69%
NK-/T-cell lymphoma	NKPI[52]	B symptoms, stage III/IV, elevated LDH, regional nodal involvement	Number of factors 0 1 2 3–4	5-y OS 81 64 34 7

NCCN, National Comprehensive Cancer Network; IPI, International prognostic index; FL, follicular lymphoma; M, mantle cell lymphoma; NK, natural killer cell; IPS, international prognostic score; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; LDH, lactate dehydrogenase; GIT, gastrointestinal tract; CNS, central nervous system; ECOG, eastern cooperative oncology group; WBC, white blood cell count; OS, overall survival; PFS, progression-free survival; FFP, freedom from progression.

History and Examination

For a patient with lymphoma, it is important to document the presence or absence of lymphoma-related constitutional symptoms (unexplained fevers of >38°C, drenching night sweats, or the unintentional loss of more than 10% of body weight over 6 months), which are more commonly associated with advanced-stage disease. Thorough physical examination, with particular attention to peripheral lymph node stations (cervical, supraclavicular, infraclavicular, axillary, epitrochlear, inguinal, and femoral) and abdomen for detection of hepatomegaly and splenomegaly, should be performed. A detailed examination of the head and neck should be performed, and if

clinical features suggestive of nasopharyngeal involvement are present, an otolaryngologist should directly visualize the region using nasal endoscopy and perform biopsies if necessary. A complete neurologic examination should also be performed, especially in cases of aggressive lymphomas, which can invade the base of skull and other cranial structures and can be sites of involvement at the time of relapse of the disease.

Laboratory Investigations

Laboratory evaluation should include complete blood count and smear, electrolytes, serum lactate dehydrogenase (LDH), β2-microglobulin, uric acid, liver function tests, serum electrophoresis and immunoglobulin levels, hepatitis B and C and HIV serology, and, in HL, erythrocyte sedimentation rate. Patients with elevated lymphocyte counts or atypical lymphocytes on peripheral blood smear should have flow cytometric analysis to determine whether peripheral blood involvement is present. In line with recently published Lugano consensus recommendations, bone marrow biopsy (BMB) can be omitted in patients with HL who undergo staging with PET-CT,[53] particularly if the intended treatment for advanced-stage patients is not influenced by the International Prognostic Score (IPS). In a study of 454 patients, no patients classified as limited stage by PET–CT were reclassified as having advanced stage by positive BMB, and only 5 (1%) were upstaged from stage III to IV.[54] This would result in a one-point increase in the IPS,[50] which could have therapeutic consequences in centers where intensified consolidation chemotherapy is given to patients with high IPS. However, in contrast to recommendations from the Lugano meeting, some believe that patients with DLBCL should still undergo BMB, because the finding of low-grade lymphoma in the marrow would influence subsequent treatment strategy.[55] In all other types of lymphomas, BMB is still recommended: a unilateral trephine biopsy of >20 mm in length, analysis of multiple levels, and appropriate immunohistochemistry make bilateral biopsies unnecessary.[56] Patients with clinical features suggestive of CNS involvement (headache, confusion, radicular pain, sensory loss, or focal neurologic lesions) should undergo lumbar puncture with detailed CSF analysis by cell count, cytology, flow cytometry, biochemistry, and microbiology.

Imaging

PET-CT is the imaging modality of choice for FDG-avid tumors, with contrast-enhanced CT scan from the head and neck to the pelvis for non–FDG-avid lymphomas. Aggressive histologies such as HL, DLBCL, Burkitt, lymphoblastic, and mantle cell lymphoma are typically FDG avid.[57] Among indolent lymphomas, FL is usually avid; however, small lymphocytic, marginal zone, and cutaneous lymphomas are less routinely avid.[58] In FDG-avid lymphomas, PET–CT changes CT-defined stage in 10% to 30% of patients, largely due to greater ability to detect extranodal disease involvement.[59,60] To evaluate suspected CNS involvement, dedicated magnetic resonance imaging (MRI) with gadolinium enhancement should be performed, with regions evaluated determined according to clinical presentation.

Treatment

The initial therapy of lymphomas in the head and neck depends on a number of factors including histologic subtype, disease stage, age, comorbidities, and performance status of the patient. In this chapter, we describe general treatment approaches for the histologies most commonly encountered in the head and neck, followed by a brief discussion of rare entities that require a specific management approach.

Classical Hodgkin Lymphoma

The current approach to initial therapy of HL considers different stages of the disease: favorable risk early-stage (I/II) disease, unfavorable risk early-stage disease, and advanced-stage disease. The precise definition of unfavorable risk early-stage disease varies slightly between study groups. For example, the National Comprehensive Cancer Network (2014) uses the presence of any one of four factors to indicate unfavorable risk: a large mass occupying more than one-third of the mediastinal width or more than 10 cm in maximal diameter, B symptoms, ESR >50 mm/hour, and more than three sites of disease. The German Hodgkin Lymphoma Study Group (GHSG) criteria are similar, but also include extranodal involvement as an adverse feature. The absence of any of these features defines favorable risk early-stage HL.

Favorable Risk Early-Stage Disease.

Favorable risk early-stage HL defines a group of patients who have an

excellent prognosis with an expected 5-year overall survival (OS) of more than 95%. The focus of therapy for these patients has been the minimization of toxicity while retaining efficacy of treatment. In patients who fulfill the GHSG criteria for favorable risk early disease, the HD10 study found that reduced intensity treatment with two (compared with four) cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 20 Gy (compared with 30 Gy) involved field radiotherapy (IFRT) did not compromise outcomes. The estimated 8-year freedom from treatment failure (FFTF) and OS were 88% and 98%, respectively.[61] In selected cases, an acceptable alternative radiation-sparing approach is four to six cycles of ABVD.[62]

Unfavorable Risk Early-Stage Disease.

Patients with unfavorable risk early-stage HL generally require four cycles of ABVD plus 30 Gy IFRT; attempts to improve outcomes by intensifying chemotherapy using bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (BEACOPP) in either standard or escalated doses have resulted in increased toxicity without improvement in progression-free survival (PFS).[63,64] Patients with nonbulky disease who decline radiation or in whom the radiation fields are deemed unacceptably toxic may receive ABVD alone for four to six cycles.[65] However, there are insufficient data on the omission of radiation in a patient with early unfavorable risk HL with a bulky mass combined modality therapy recommended in such cases.

Advanced-Stage Disease.

Patients with advanced-stage HL require prolonged induction chemotherapy, with choices including ABVD, $\text{BEACOPP}_{\text{baseline}}$, and $\text{BEACOPP}_{\text{escalated}}$. The only study to date that has directly compared the two regimens randomized patients to receive six cycles of ABVD or eight cycles of BEACOPP (four escalated, four baseline).[66] They found superior 7-year freedom from progression (FFP) in the BEACOPP arm (85% vs. 73%, $p = 0.004$), but OS was not significantly different (89% vs. 84%, $p = 0.39$). The lack of difference in OS was attributed to both ability to successfully salvage patients experiencing disease relapse after ABVD and the increased acute and long-term toxicity in patients treated with BEACOPP. Although a recent network

meta-analysis of 14 studies reported that $\mathrm{BEACOPP}_{escalated}$ × 6 cycles was associated with a 10% OS advantage over ABVD,[67] expert opinion remains divided. However, until direct comparisons demonstrate a survival benefit for $\mathrm{BEACOPP}_{escalated}$ over ABVD, both regimens remain reasonable choices for treatment of this group; however, because BEACOPP induces more toxicity than does ABVD, without clearly defined survival advantage, most clinicians at major centers in the United States still administer ABVD to patients with advanced presentations of HL.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) carries a better prognosis than does classical HL. Patients with NLPHL constituted 4.8% of all patients treated on the GHSG HD4 to HD12 studies.[68] Compared with classical HL, patients with NLPHL were more likely to achieve CR, were less likely to experience disease progression, and had lower treatment-related mortality than did patients with classical HL. Due to the relative rarity of these patients, data supporting treatment decisions are based largely on prospective phase II and retrospective studies.

Limited-Stage Disease.

Most patients (70% to 80%) with NLPHL have limited-stage disease at diagnosis, and enlarged lymph nodes in the head and neck area are frequently the only involved site at disease presentation. Patients with stage IA NLPHL have excellent outcomes using radiation therapy alone, with an estimated 15-year FFP of 85%.[69] A recent retrospective analysis from the British Columbia Cancer Agency (BCCA) suggested that combined modality with two cycles of ABVD followed by IFRT resulted in improved PFS and OS compared to results from a group of patients who received only radiation therapy.[70] Patients with stage IB or II disease are generally treated with chemotherapy in addition to radiation; however, direct comparisons between regimens have been precluded by the rarity of the disease. Strategies vary from center to center, although the BCCA approach (two ABVD followed by IFRT) is reasonable.

Advanced-Stage Disease.

Patients with NLPHL and classical HL with advanced-stage disease treated with identical regimens on GHSG HD4 to HD12 studies had similar FFTF results (77% vs. 75%, p = 0.46) with median observation of 50 months.[68] However, given that rituximab has activity in this entity,[71] an alternative approach would be to administer rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), the same regimen used to treat other types of B-cell lymphomas that express CD20 on the tumor cell surface. In a retrospective analysis of 63 patients with NLPHL conducted at MD Anderson Cancer Center, 24 had advanced-stage disease, and 12 received R-CHOP. All patients had a response (90% CR) and no progressions have occurred, with a median observation of 42 months.[72] No prospective, randomized comparisons are possible, but the regimen appears at least as effective as regimens used in classical HL and requires validation in a larger cohort of patients.

Diffuse Large B-Cell Lymphoma

This histologic subtype describes a group of tumors with diverse molecular and clinical features. CHOP constituted the backbone of therapy in this disease for many years[73] until the anti-CD20 monoclonal antibody rituximab was established as a highly effective agent in patients with CD20-positive lymphomas.[74] Subsequent phase III studies demonstrated that the addition of rituximab to CHOP (R-CHOP) improved CR, PFS, and OS rates compared to results obtained with CHOP alone, establishing R-CHOP as a standard of care.[75,76] For older patients (>65 years of age) with DLBCL, R-CHOP remains the standard of care, given every 2 (R-CHOP14) or 3 weeks (R-CHOP21). No significant difference in outcome has been demonstrated between these two schedules, as two large, randomized studies have found no significant differences in outcomes with treatment consisting of six cycles of R-CHOP14 (with 8 doses of rituximab) or eight cycles of R-CHOP21.[77,78]

In younger patients (<65 years of age), most attempts to improve outcomes using more intensive chemotherapy have met with increased toxicity without improvements in efficacy.[76,79] A notable exception to this rule was a French randomized study comparing rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisolone (R-ACVBP) and R-CHOP21 for patients aged 18 to 59 with an IPI score of at least 1.[80]

Patients randomized to R-ACVBP had superior 3-year PFS (91% vs. 67%, $p = 0.0035$) and OS (92% vs. 84%, $p = 0.007$). However, the toxicity was considerably higher: febrile neutropenia was seen in 38% of those receiving the more intensive regimen versus 9% with standard R-CHOP. This fact, as well as difficulty accessing vindesine outside Europe, has limited widespread adoption of this regimen in Western countries. Furthermore, physician familiarity, outpatient deliverability, and predictability of adverse events with R-CHOP all contribute to its durability in practice. Dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) has been effective in phase II studies although patients with activated B-cell DLBCL still have inferior outcomes.[81,82] A phase III randomized study conducted by Cancer and Leukemia Group B (CALGB) comparing R-CHOP with R-EPOCH in patients with previously untreated DLBCL, with a primary endpoint of 5-year EFS (NCT00118209) with molecular correlative analysis will clarify the best use of these regimens.

Special Cases of Diffuse Large B-Cell Lymphoma

Limited-stage (I/II) disease.

Patients with limited-stage disease constitute 30% to 40% of patients with DLBCL. Patients with bulky (>10 cm) or stage IIB disease should be treated as having advanced-stage disease (see above). Nonbulky limited-stage patients can be treated with three cycles of R-CHOP21 plus IFRT or six to eight cycles of R-CHOP21 without radiation as outcomes using either approach are excellent, with 3-year PFS results of ~90%.[76,83] Therefore, the choice between these approaches is made with the intention of minimizing treatment-related toxicity. Factors that should be considered include the location of the radiation field, age and comorbidities of the patient, and patient and physician preference. Radiation alone is not recommended, as outcomes are inferior compared with combined modality therapy.[84–86]

Double-hit lymphoma.

Patients with “double-hit” lymphomas (whether defined by gene rearrangements or immunohistochemistry of both *MYC* and *BCL2* or *BCL6*) have particularly aggressive clinical behaviors with poor outcomes with R-CHOP chemotherapy.[87,88] CNS involvement appears to be higher in these patients compared to those without “double-hit” disease, though the

magnitude of this risk varies widely between studies.[37,89–94] Nonetheless, such patients should undergo baseline evaluation for CNS involvement. Given the rarity of the disease, prospective data are lacking; however, a retrospective analysis of 129 cases from MD Anderson Cancer Center provides some insights.[93] The 2-year EFS rates in patients treated with R-CHOP (n = 57), R-Hyper-CVAD (n = 34), and R-EPOCH (n = 28) were 25%, 32%, and 67%, respectively. Among those patients who achieved CR, there was no apparent difference in 2-year EFS (68% vs. 53%, p = 0.13) or OS (70% vs. 70%, p = 0.563) for patients who received ASCT consolidation following induction of remission compared to those who did not. However, at the present time, the approach at MD Anderson Cancer Center is to administer induction therapy with R-EPOCH with the addition of CNS-directed prophylaxis followed by consolidation with stem cell transplant in the majority of cases.

Primary mediastinal B-cell lymphoma.

Patients with primary mediastinal B-cell lymphoma (PMBL) are typically young and female and may present with supraclavicular lymphadenopathy and evidence of superior vena cava obstruction. Although R-CHOP is an acceptable treatment provided radiation is also used,[95] a phase II trial of 51 patients using R-EPOCH (largely without radiotherapy) achieved excellent EFS of 93% and OS of 97% after a median observation period of 5 years.[96] Because this approach avoids the risk of radiation-induced cardiac morbidity and second malignancies, this currently is considered the preferred approach for therapy of PMBL.

Marginal Zone/MALT Lymphoma.

Extranodal marginal zone or MALT lymphomas frequently involve sites in the head and neck including ocular adnexal structures, salivary glands, and thyroid. Patients with this disease have excellent outcomes regardless of therapy: a retrospective International Extranodal Lymphoma Study Group (IELSG) series of nongastric MALT reported a 5-year OS of 90% irrespective of treatment.[97] There is no clear standard of care, with treatment options including radiation alone, chemotherapy, or rituximab and eradication with antibiotics. Surgery alone is not the treatment of choice, although the diagnosis may only become apparent after resection has been performed. If there is no evidence of recurrent disease, observation is

sufficient; however, patients with positive resection margins may be offered radiation to minimize the risks of recurrence. MALT lymphoma is exquisitely radiosensitive, and radiotherapy at doses of 24 to 32 Gy results in excellent response rates and long-term disease control.[98] Due to the frequent presence of *C. psittaci* infection in orbital and ocular adnexal MALT lymphomas, the IELSG conducted a phase II study of doxycycline alone as therapy for this disease, administering 100 mg oral twice weekly for 3 weeks.[16] The treatment was safe and effective with an OS of 65%, but responses took some time to achieve, with best responses attained at 6 months. The 5-year PFS rate for patients treated in this study was 55%. Chemotherapy with alkylating agents such as cyclophosphamide or chlorambucil either alone or in combinations (e.g., cyclophosphamide, vincristine, prednisolone [CVP]) is well tolerated and effective.[99] Single-agent rituximab provides a response rate of 70% in this entity and when added to chlorambucil improves CR and EFS rates (but not OS) compared to chlorambucil alone.[100]

Follicular Lymphoma.

For therapeutic purposes, patients with FL are considered in three main groups: limited stage (I/II) and advanced stage with either low or high tumor burden.

Limited-stage disease.

Only 15% to 30% of patients have limited-stage disease at diagnosis. The standard of care for limited-stage disease is radiotherapy, which results in excellent local tumor control and 10-year PFS of ~50%, suggesting that a proportion of these patients are potentially cured of their disease.[101,102] However, much of the published data are retrospective, and there is some evidence that adding combined modality therapy may improve outcomes. Seymour et al.[103] treated 85 patients with limited-stage indolent NHL (mostly FL) with CHOP/CVP + bleomycin followed by 30 to 40 Gy IFRT and observed 10-year FFS and OS rates of 72% and 80%. An ongoing cooperative group study by the Australasian Leukemia and Lymphoma Group and Trans-Tasman Radiation Oncology Group comparing IFRT ± CVP is ongoing (NCT00115700). Three small retrospective series have described long-term outcomes (collectively around 100 patients) with asymptomatic localized FL who have undergone observation alone.[104–106] A

retrospective analysis from Stanford reported a 10-year OS rate of 85%, with 63% of patients not having required any therapy after a median follow-up of 7.2 years. These data lend qualified support that this approach is reasonable.

Low-tumor burden, advanced-stage disease.

Patients with advanced-stage disease (stage III/IV) constitute the majority of patients with FL. The decision on when to initiate treatment was established in the prerituximab era in two studies that randomized patients to observation or treatment and found no difference in OS for early treatment.[107,108] These criteria remain widely used in both practice and clinical trials today (Table 26.6). A recent international phase III study of 379 patients recently compared observation only (n = 187) with rituximab induction only (n = 84, arm closed early) or rituximab induction followed by maintenance for 2 years (n = 192).[109] The number of patients not needing treatment at 3 years was 46%, 78%, and 88% in observation, rituximab induction, and maintenance arms, respectively ($p < 0.0001$), although there was no difference in OS rates, probably because patients with FL usually have chemosensitive disease at first relapse. Patients randomized to maintenance reported improvements in patient-reported outcomes. Finally, the ECOG E4402 (RESORT) study compared two schedules of rituximab in asymptomatic low–tumor burden patients.[110] They treated 289 patients using 4 doses of weekly rituximab as induction; patients were then randomized to re-treatment at progression or maintenance rituximab given every 3 months, with both strategies continued until treatment failure. There was no difference in time to treatment failure (TTF) between the two strategies, suggesting that the re-treatment approach was as effective while using less rituximab. Although these two studies demonstrate that rituximab is a reasonable treatment option in patients with asymptomatic low–tumor burden FL, there remains no evidence of a benefit in OS using this approach, and observation of the asymptomatic patient with advanced disease still remains a viable option of management (**Table 26.7**).

Table 26.7 Criteria for the Initiation of Treatment in Patients with Advanced-Stage Follicular Lymphoma

GELF Criteria[108]	BNLI Criteria[107]
ALL of the following: ■ Maximum diameter of disease <7 cm ■ Fewer than three nodal sites ■ No systemic symptoms ■ Spleen <16 cm on CT ■ No significant effusions ■ No risk of local compressive symptoms ■ No circulating lymphoma cells ■ No bone marrow compromise (Hb < 10 g/dL, WBC count < 1.5 × 10^9/L, platelet count < 100 × 10^9/L)	NONE of the following: ■ B symptoms or pruritus ■ Rapid generalized progression of disease ■ Bone marrow compromise (Hb ≤ 10 g/dL, WBC count < 3.0 × 10^9/L, or platelet count < 100 × 10^9/L) ■ Life-threatening organ involvement ■ Renal infiltration ■ Bone lesions

GELF, Groupe pour L'Etude de Lymphome Folliculaire; BNLI, British National Lymphoma Investigation; CT, computed tomography; Hb, hemoglobin; WBC, white blood cell.

High-tumor burden, advanced-stage disease.

Rituximab-based chemoimmunotherapy is considered the standard of care for symptomatic patients with FL. Common chemotherapy backbones include CHOP, CVP, bendamustine, and fludarabine-based regimens. The Italian FOLL05 study randomized 534 untreated patients with FL to eight cycles of R-CVP, six cycles R-CHOP, or six cycles of R-FM (fludarabine and mitoxantrone).[111] Three-year TTF results were 46%, 62%, and 59% in the R-CVP, R-CHOP, and R-FM arms, respectively. Although both R-CHOP and R-FM were superior to R-CVP in terms of disease control, R-FM resulted in higher rates of grade III/IV neutropenia and a higher number of second malignancies. Two large studies with a noninferiority design have compared bendamustine–rituximab (BR) with R-CHOP. Rummel and colleagues randomized 549 patients with untreated indolent lymphoma (54% FL) to BR or R-CHOP.[112] Among patients with FL, the median PFS was not reached for the BR arm, compared with 40.9 months for patients who received R-CHOP (hazard ratio 0.61; 95% CI 0.42 to 0.87; p = 0.0072). The BRIGHT study randomized 447 patients with indolent NHL to BR or R-CHOP/CVP.[113] BR was noninferior to R-CHOP/CVP in terms of response rates; however, the more clinically relevant secondary endpoints of PFS and OS were not mature at the time of initial report. Therefore, we consider either BR or R-CHOP as appropriate induction therapy for patients with high–tumor burden FL. BR has some advantages because it appears at least as effective as R-CHOP and less toxic; however, if there is clinical or pathologic uncertainty about whether a large-cell component may be present (such as a rapidly enlarged discordant lymph node growth, serum LDH >2 × upper limit of normal,

$SUV_{max} > 15$), R-CHOP is preferred, as the outcome is poor in patients with DLBCL treated with BR.[114]

Maintenance rituximab.

Treatment with maintenance rituximab following induction with chemoimmunotherapy is supported by two large studies. In the ECOG E1496 study, investigators treated patients who had stage III/IV indolent B-cell NHL (73% FL) with CVP; responders were randomized to receive either maintenance rituximab or observation.[115] Maintenance improved the depth of response and PFS rates, with a nonsignificant trend toward benefit in OS [HR 0.6 (0.4 to 1.1, $p = 0.05$)]. In the PRIMA study, patients received R-chemoimmunotherapy as induction [R-CVP (23%), R-CHOP (74%), or R-FCM (4%)] and then received either rituximab maintenance or observation.[116] Patients receiving maintenance had better PFS results than those who did not, and at a recent update, with a median follow-up of 73 months from randomization, the 6-year PFS rate was 42.7% for the observation arm and 59.2% for the maintenance arm ($p < 0.001$), with consistent benefits regardless of FLIPI risk groups, age, sex, induction chemotherapy, and type of response to induction.[117] Similar to outcome in the ECOG study, there was no benefit yet reported in OS. The RESORT study has shown that rituximab retreatment results in similar TTF with much less rituximab use than a maintenance strategy after single-agent rituximab induction in low–tumor burden patients: whether the same is true in symptomatic patients with high tumor burden treated with chemoimmunotherapy induction remains to be seen. Until then, such patients should receive maintenance rituximab if improved PFS is the goal of treatment.

Extranodal NK-/T-Cell Lymphoma, Nasal Type.

Previously described as “lethal midline granuloma,” this is an aggressive EBV-positive extranodal NK-/T-cell neoplasm characterized by relentless ulcerative destruction of the nose and deep midfacial structures and angioinvasion. Extranodal NK-/T-cell lymphoma (ENKTL), nasal type, is most common in Asia and Central and South America.[118] An EBV-driven hemophagocytic syndrome is reported in <5% of cases, but it is important to recognize as it can be rapidly fatal if unrecognized and untreated. The clinical

features include high fevers, pancytopenia, hepatosplenomegaly, and very high serum ferritin levels.[119] Treatment requires the use of an etoposide containing chemotherapy regimen plus high-dose steroids or intravenous immunoglobulin. Histologically, necrosis is common and hampers diagnosis; therefore, surgeons should take as large and representative a biopsy as safely possible, with material sent fresh to the laboratory. The NK-/T-cell lymphoma prognostic index (NKPI) was derived from a large series of Korean patients (see Table 26.1).[52] Higher pretreatment plasma EBV DNA level number predicts inferior outcome,[120] and levels can be used to monitor response to therapy and predict recurrence.[118]

Around 70% to 80% of patients have localized (IE/IIE) disease, and chemoradiotherapy is the preferred approach. NK cells have high levels of P-glycoprotein; thus, ENKTL are frequently highly resistant to drugs amenable to cellular export using this mechanism.[121] Responses to CHOP are suboptimal, and many patients actually experience kinetic failure between cycles.[122] A combination of dexamethasone, etoposide, and ifosfamide with carboplatin (DeVIC) with concurrent radiotherapy developed by the Japanese cooperative group has produced encouraging results, with CR rates of 77% to 80% and a 70% 5-year OS rate.[123] A Korean protocol that uses dexamethasone, etoposide, and ifosfamide cisplatin (VIPD) achieved similar results.[124] L-asparaginase-based regimens such as GELOX (gemcitabine, L-asparaginase, and oxaliplatin) and the more intensive SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) both sandwiched with IFRT have resulted in high response rates and durable remissions. SMILE in particular is associated with considerable hematologic toxicity and a toxic death rate of 7%.[125] In advanced-stage patients, multiagent chemotherapy using L-asparaginase-based regimens such as SMILE and L-asparaginase, methotrexate, and dexamethasone is the treatment of choice.[126,127]

SUMMARY

The lymphomas are a group of malignancies with widely heterogeneous biologic and clinical manifestations. The incidence of lymphomas in the United States is rising, and their effects on mortality in the young and in productive adults are important. The prognosis varies widely according to the

histology, tumor burden, age, and performance status of the patient. Specific prognostic indices have been developed and validated in many histologic subtypes. Because correct diagnosis is critical for appropriate management, effort should be made to obtain an optimum pathologic specimen by surgical excision. The success of the pathologist in appropriately diagnosing the disease rests in part on the technical skill of the surgeon in removing and handling the surgical specimen. A rapid increase in information regarding the genetic and molecular pathogenesis of various lymphoma subtypes has resulted in greater precision and refinement of diagnostic and management strategies.

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27 Sarcomas and Soft Tissue Tumors of the Head and Neck

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Sarcomas of the head and neck are a varied group of malignancies with widely differing clinical courses and clinical outcomes. Head and neck sarcomas arise from mesenchymal elements within the head and neck, including deep soft tissues, bone, and cartilage. Approximately 15% of all sarcomas arise within the head and neck, yet only 1% of all head and neck malignancies are sarcomas.[1,2]

Sarcomas are frequently categorized by their cell of origin and are generally broadly grouped into soft tissue sarcomas and bone/cartilaginous. More than 50 subtypes of sarcomas defined on the basis of histologic are recognized by the World Health Organization (WHO) (**Table 27.1**).[3] Alternatively, sarcomas may be categorized according to their histologic grade, which may inform treatment decisions more directly than cell of origin does. For example, high-grade sarcomas are more likely to require complex multidisciplinary treatment plans.

Table 27.1 Etiologic Factors for Head and Neck Sarcomas

Genetic Predisposition	Gene(s)	Sarcoma(s)
Li-Fraumeni syndrome	TP53	Bony and soft tissue sarcomas
Hereditary retinoblastoma	Rb	Osteosarcoma
DMS-MFH	LOH at 9p21-22	Malignant fibrous histiocytoma (MFH)
Werner syndrome	WMN	Bony and soft tissue sarcomas
Gardner syndrome	APC	Desmoid tumors
Neurofibromatosis type 1	NF1	MPNST
Costello syndrome	HRAS	Rhabdomyosarcoma
Beckwith-Wiedemann syndrome	CDKN1, IGF2, H19, KCNQ1OT1	Rhabdomyosarcoma
Rothmund-Thompson syndrome	RECQL4	Osteosarcoma
Paget disease	Unknown	Osteosarcoma
Ollier and Maffucci syndromes	IDH1, IDH2	Chondrosarcoma
Environmental Exposures		**Sarcoma(s)**
Ionizing radiation		Bony and soft tissue sarcomas
HIV, HHV-8		Kaposi Sarcoma
Industrial waste		Bony and soft tissue sarcomas
Herbicides and chlorophenols		Bony and soft tissue sarcomas

DMS-MFH, diaphyseal medullary stenosis with malignant fibrous histiocytoma; HLRCC, hereditary leiomyomatosis and renal cell cancer; MPNST, malignant peripheral nerve sheath tumors.

For the vast majority of sarcomas, the etiology of the tumor is not known. Some genetic and environmental factors have been associated with development of sarcomas. For example, although very rare, several inherited syndromes are well known to increase the risk of specific types of sarcomas (**Table 27.2**). Germline mutations in the tumor suppressor gene *TP53*, such as those occurring in Li-Fraumeni syndrome, have been linked to an increased risk of both soft tissue and osteosarcomas.[4,5] Diamond-Blackfan syndrome, a hereditary anemia linked to mutations in genes encoding ribosomal proteins, has been associated with osteosarcoma.[6,7] Malignant fibrous histiocytoma (MFH) arising in bone occurs in up to 35% of patients with the rare cancer syndrome, diaphyseal medullary stenosis with MFH, and is characterized by loss of heterozygosity at the chromosomal band 9p21-22.[8] Werner syndrome, characterized by rapid aging and mutations in the WMN gene, is well known to be associated with an increased incidence of multiple sarcoma types.[9] Gardner syndrome, characterized by *APC* mutations and hereditary colon polyposis and cancer, is associated with an increased incidence of desmoid fibromatoses.[10]

Table 27.2 Histologic Subtypes of Head and Neck Sarcomas with

Known Genetic Alterations

WHO Sarcoma Histologic Subtypes	Cytogenic Alterations	Altered Gene(s)
Adipocytic Tumors		
Dedifferentiated liposarcoma	Supernumerary ring and giant marker chromosomes, amplification 12q13-15	MDM2, CDK4, HMGA2, SAS, GL1
Myxoid/round cell liposarcoma	t(12;16)(q13;p11), t(12;22)(q13;q12)	FUS-DD1T3, EWSR1-DD1T3
Pleomorphic liposarcoma	Complex alterations	
Fibroblastic, Myofibroblastic, and Fibrohistiocytic Tumors		
HPC/SFTs	Complex alterations	NAB2–STAT6
Fibrosarcoma	Complex alterations	
Myxofibrosarcoma	Complex alterations	
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11), t(11;16)(p11;p11)	FUS-CREB3L2, FUS-CREB3L1
Sclerosing epithelioid fibrosarcoma		EWSR1-CREB3L1
Undifferentiated pleomorphic sarcoma/MFH		
Desmoid fibromatosis	Trisomy 8 or 20; Loss of 5q21	CTNNB1 or APC mutations
DFSPs	t(17;22)(q21;q13) and derivative ring chromosomes	COL1A1-PDGFB
Smooth Muscle Tumors		
Leiomyosarcoma	Complex alterations	
Skeletal Muscle Tumors		
Embryonal rhabdomyosarcoma	LOH at 11p15	
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14), t(1;13)(p36;q14), t(X;2)(q13;q35)	PAX3-FKHR and PAX7-FKHR
Pleomorphic rhabdomyosarcoma	Complex alterations	
Vascular Tumors		
Epithelioid hemangioendothelioma	t(1;3)(p36.3;q25)	
Angiosarcoma	Complex alterations	PTPRB and PLCG1 mutations
Tumors of Peripheral Nerves		
Malignant peripheral nerve sheath tumors	Complex alterations	
Tumors of Uncertain Differentiation		
Synovial sarcoma	t(X;18)(p11;q11)	SS18-SSX1, SS18-SSX2, SS18-SSX4
Alveolar soft-part sarcoma	der(17)t(X;17)(p11;q25)	ASPL-TFE3
Sarcomas of Cartilage and Bone		
Chondrosarcoma	Complex alterations	
Osteosarcoma	Complex alterations	
PNET/Ewing sarcoma	t(11;22)(q24;q12), t(21;22)(q22;q12), t(2;22)(q33;q12), t(7;22)(p22;q12), inv(22)(q12;q12), t(16;21)(p11;q22)	EWS-ETS

The best characterized environmental risk factors linked to sarcoma development include the link between HIV infection and HHV8-induced Kaposi sarcoma (KS). Rarely, sarcoma can arise in the setting of prior exposure to ionizing radiation. Less well-established associations have been documented between increased sarcoma risk and environmental exposure to chlorophenols, herbicides, and certain chemicals in industrial waste products.[11]

PRINCIPLES OF SARCOMA MANAGEMENT

Patient Evaluation

Symptoms and clinical presentations in patients with sarcoma vary widely according to the histologic subtype and tumor location, but several sarcoma types have characteristic presentations. For instance, angiosarcomas typically present as a violaceous plaque on the scalps of elderly white males, whereas a chondrosarcoma often presents as a destructive bony lesion centered on the cricoid. The majority of types of sarcoma, however, lack a specific characteristic presentation and frequently present with an asymptomatic mass.[11] In a review of over 2,000 patients presenting to MD Anderson Cancer Center over the past 44 years (**Tables 27.3 and 27.4**), the most frequent locations for sarcomas arising in the head and neck of adults (Table 27.3) included the scalp/face (30% of cases), followed by the sinonasal cavity/anterior skull base (23%) and the upper aerodigestive tract and the parotid/neck (each accounting for 19%). Sarcomas arising in the ear/lateral or posterior skull base were quite rare (<8%). In the pediatric and adolescent population (Table 27.4), the distribution of sites is somewhat different with the sinonasal cavity/anterior skull base accounting for 28% of cases and the upper aerodigestive tract for 27% followed by the scalp/face (22%), the parotid/neck (14%), and the ear/lateral or posterior skull base (9%).

Table 27.3 Adult Head and Neck Sarcomas at the University of Texas MD Anderson Cancer Center (Age ≥ 18, 1970–2013)

Histologic Type	No.	%	Site of Origin				
			Scalp and Face	Sinonasal Tract Anterior/Medial Skull Base	Ear Lateral/ Posterior Skull Base	Upper Aerodigestive Tract	Parotid and Neck
Bone and Cartilage							
Osteosarcoma	288	14.8	3	108	48	125	4
Ewing sarcoma/PNET	35	1.8	5	10	9	5	6
Chondrosarcoma	153	7.9	2	45	52	46	8
Fibrous							
Undifferentiated pleomorphic sarcoma/MFH	159	8.2	59	27	10	17	46
Fibrosarcoma	49	2.5	10	16	0	11	12
Fibromyxoid sarcoma	4	0.2	1	0	0	0	3
DFSP	110	5.7	89	0	1	0	20
Muscular							
Rhabdomyosarcoma	199	10.3	22	112	1	52	12
Leiomyosarcoma	72	3.7	17	14	2	15	24
Vascular							
Angiosarcoma	240	12.4	209	8	4	6	13
Hemangiopericytoma	53	2.7	11	21	2	7	12
Kaposi sarcoma	37	1.9	17	0	1	6	13
Neural							
Neurogenic sarcoma	72	3.7	18	7	0	4	43
Fatty							
Liposarcoma	38	2.0	7	4	0	5	22
Histogenesis Unclear							
Synovial sarcoma	72	3.7	14	3	1	21	33
Alveolar soft part sarcoma	12	0.6	2	3	0	4	3
Unclassified and Other	348	17.9	99	70	21	55	103
Head and Neck Sarcoma (Totals)	1941	100	585	448	152	379	377

Table 27.4 Pediatric Head and Neck Sarcomas at the University of Texas MD Anderson Cancer Center (Age < 18, 1970–2013)

Histologic Type	No.	%	Site of Origin				
			Scalp and Face	Sinonasal Tract Anterior/Medial Skull Base	Ear Lateral/ Posterior Skull Base	Upper Aerodigestive Tract	Parotid and Neck
Bone and Cartilage							
Osteosarcoma	30	7.5	0	1	8	21	0
Ewing sarcoma/PNET	25	6.3	5	5	8	4	3
Chondrosarcoma	10	2.5	0	6	3	1	0
Fibrous							
Undifferentiated pleomorphic sarcoma/MFH	8	2.0	3	1	2	1	1
Fibrosarcoma	10	2.5	5	0	0	3	2
Fibromyxoid sarcoma	1	0.3	0	0	0	1	0
DFSP	5	1.3	5	0	0	0	0
Muscular							
Rhabdomyosarcoma	228	57.6	60	82	13	54	19
Leiomyosarcoma	2	0.5	0	1	0	1	0
Vascular							
Angiosarcoma	1	0.3	0	0	0	1	0
HPC	4	1.0	1	1	1	0	1
Neural							
Neurogenic sarcoma	13	3.3	4	0	1	0	8
Fatty							
Liposarcoma	2	0.5	0	1	0	1	0
Histogenesis Unclear							
Synovial sarcoma	9	2.3	0	0	0	3	6
Alveolar soft part sarcoma	6	1.5	0	1	0	3	2
Unclassified and other	42	10.6	6	12	1	11	12
Head and neck sarcoma (totals)	396	100	89	111	37	105	54

The physical examination in a patient with a known or suspected sarcoma should entail a careful assessment of the extent of the disease, the degree of fixation to surrounding structures, and the presence or absence of regional adenopathy. Cross-sectional imaging should be performed to further delineate the extent of the primary lesion and to assess for regional and distant spread of disease. For most head and neck sarcomas, distant metastases are most likely to present in the lungs, and chest imaging with computed tomography should be obtained routinely. For sarcomas with a higher risk of intracranial metastases, such as alveolar soft part sarcoma (ASPS) and angiosarcoma, the staging workup should include imaging of the brain.[12]

Although fine needle biopsy is the initial biopsy of choice for many head and neck masses, biopsy for head and neck sarcomas often entails either a core needle or incisional biopsy as the limited amount of tissue and lack of tissue architecture provided by fine needle aspiration makes diagnosis of

sarcomas particularly difficult. Biopsy sites should be planned such that they can be easily excised during subsequent surgical resection. Pathologic assessment of the biopsy specimen should be undertaken by a pathologist with experience in sarcomas[13] with the goal of providing information on the histologic subtype as well as tumor grade at a minimum. Standard morphologic assessment remains the standard for diagnosis, although the use of cytogenetics to augment standard morphologic assessment is accelerating (Table 27.1). For consistency and communication among providers, pathologic reports should use the nomenclature for sarcomas standardized by the WHO.[3] Approximately one-quarter of head and neck sarcomas arising in adults are unclassified and undifferentiated, high-grade, pleomorphic sarcomas, with osteosarcomas, angiosarcomas, and rhabdomyosarcomas accounting for another one-third (Table 27.3). However, in children and adolescents, the majority are rhabdomyosarcomas (Table 27.4).

Staging and Prognostic Factors in Head and Neck Sarcomas

The American Joint Committee on Cancer staging system for soft tissue sarcomas incorporates measures of tumor size (> or ≤5 cm), location with respect to deep fascial planes, the presence of regional or distant metastatic spread, and tumor grade. For sarcomas located in the head and neck, the usefulness of this staging system has been questioned, as such tumors are typically smaller than 5 cm at the time of presentation and have high rates of deep fascial involvement.[1,14]

For most histologic subtypes of sarcoma, studies have shown that location within the head and neck portends a worse prognosis than location in other anatomic regions.[15] Tumor grade and margin status remain the most consistently identified prognostic factors in multiple case series of head and neck sarcomas.[1,16–18] Unfortunately, the proximity to vital structures frequently precludes wide resection margins for head and neck sarcomas, a factor that has been linked to their poor prognosis. In addition to grade and margin status, tumor size, age, and smoking status have been associated with reduced survival.[15–19] The prognostic significance of regional metastatic spread for head and neck sarcomas is debated.[14,20]

Principles of Surgery

The traditional cornerstone of therapy for head and neck soft tissue and bony sarcomas without evidence of distant metastatic disease on presentation is surgical excision with histologically negative margins. Given the propensity for microscopic spread beyond the clinically apparent tumor, margins of 2 cm and inclusion of an adjacent normal-appearing tissue plane beyond the mass should be attempted. Surgical resections should be planned to include excision of the biopsy site. Within the head and neck, proximity of critical structures frequently precludes obtaining wide margins. If close or histologically positive surgical margins are anticipated on the basis of preoperative clinical and radiologic evaluation, neoadjuvant chemotherapy and/or preoperative radiation therapy should be considered.[12] Standard terms used to describe surgical margins for sarcomas are *R0* for microscopically negative margins, *R1* for microscopically positive margins, and *R2* for grossly positive margins.

Head and neck sarcomas should be managed by experienced multidisciplinary teams with experience in treating sarcomas. Surgical management of head and neck sarcomas frequently involves multispecialty surgical teams including thoracic, vascular, reconstructive, ophthalmologic, and neurosurgical services, but regardless of which other specialists are involved, an experienced head and neck surgeon is essential. Given the frequent need for adjuvant chemotherapy and radiation therapy either before or after surgery, close coordination with medical and radiation oncologists with experience treating sarcomas is critical.

Principles of Radiation Therapy

For head and neck sarcomas, preoperative or postoperative adjuvant radiation therapy is typically given as part of combined modality primary local therapy for nonmetastatic presentations. Multiple case series have demonstrated improved local control with the use of adjuvant radiation therapy in cases of positive margins or high-grade tumors.[21,22] Unfortunately, negative margins can be difficult to achieve in head and neck sarcoma surgery; in some series, up to half of patients have R1 or R2 resections.[11] Low-grade sarcomas with wide negative margins may be considered for single-modality treatment with surgery alone.

Although the benefits of adjuvant radiation therapy for sarcomas in the head and neck are widely accepted, the optimal timing of radiation therapy remains controversial. Both preoperative and postoperative radiation therapies have potential advantages. Tumor margins and the regions that need to be targeted with radiation are more easily defined before surgical resection, when the sarcoma mass is present during simulation. Consequently, preoperative radiation therapy has the advantages of a lower dose (50 Gy vs. 60 to 66 Gy for postoperative radiation therapy) and a smaller, precisely defined radiation field, translating into a lower risk of late radiation-related side effects, including fibrosis and edema, and the potential to minimize the radiation dose to critical structures.[23] However, preoperative radiation therapy has been reported to be associated with increased wound complications following surgery. In a randomized trial that attempted to address this issue, 190 patients with soft tissue sarcoma of the extremities were randomized to preoperative or postoperative adjuvant radiation therapy.[24] Similar rates of local control, disease-free survival, disease-specific survival, and overall survival were noted between the groups. Among patients with lower extremity sarcomas, wound complications were more common in patients undergoing preoperative radiation therapy. While late side effects of radiation therapy are presumed to be lower with lower doses used preoperatively then with postoperative doses, long-term side effects have not been reported for this trial. In a separate analysis of 40 consecutive patients with head and neck soft tissue sarcomas treated with preoperative radiation therapy, the rate of wound complications was lower than that reported previously for soft tissue sarcomas of the extremities,[25] suggesting that the improved blood supply of the head and neck may reduce the risk of some of the wound complications associated with preoperative radiation therapy at other sites. The use of preoperative radiation therapy should be considered in all cases of sarcoma of the head and neck where radiation will be used and the complication risk for surgery in an irradiated field does not preclude it.[26] This requires treatment plan coordination and discussion between the treating radiation oncologist and the head and neck surgeon.

Principles of Chemotherapy

For sarcomas that display evidence of distant metastatic spread,

chemotherapy is generally indicated and is individualized on the basis of specific tumor histologic features.[26] For localized resectable sarcomas in adults, the role of chemotherapy remains less well defined. The Sarcoma Meta-analysis Collaboration analyzed results from 14 trials evaluating doxorubicin-based therapy in resectable soft tissue sarcomas. Local, distant, and overall recurrence-free survival times were significantly improved with doxorubicin-based adjuvant chemotherapy, although the absolute improvement in overall recurrence-free survival was only 6% to 10% at 10 years.[27] Other trials have demonstrated histologic subtype–specific responses to different chemotherapeutic agents and are discussed below. Authors increasingly describe the use of chemotherapy to treat sarcomas, particularly the use of neoadjuvant chemotherapy for high-risk tumors.

SOFT TISSUE SARCOMAS

Soft Tissue Tumors of Endothelial Origin

Angiosarcoma

Angiosarcomas are rare soft tissue sarcomas arising from endothelial cells. They classically present as a violaceous macule or papule on the scalp in elderly white males, although they can present in people of any age, gender, or ethnicity and in any anatomic location. Most angiosarcomas in the head and neck arise spontaneously in the elderly, although several well-known risk factors are associated with the development of angiosarcomas at other sites in the body. These risk factors include chronic lymphedema following treatment for breast cancer (Stewart-Treves syndrome), prior radiation exposure, and prior exposure to environmental toxins such as vinyl chloride, thorium dioxide, anabolic steroids, arsenic, and radium.[28] Susceptibility to angiosarcoma has been proposed to be increased in people with mutations in *BRCA1* and *BRCA2*, neurofibromatosis, Maffucci syndrome, and Klippel-Trenaunay syndrome. Up to 38% of cases of angiosarcoma harbor mutations in *PTPRB* or *PLCG1*.[29]

Frequent delays in diagnosis are common for head and neck angiosarcomas given their propensity to mimic benign conditions, including bruises and benign vascular lesions, typically of the scalp (**Fig. 27.1**, Table

27.3). Angiosarcomas, particularly those of the scalp, have a propensity for diffuse spread beyond the visible cutaneous abnormality, making underestimation of the true extent of disease commonplace. Satellite lesions occur in up to half of patients and portend a worse prognosis.[30] Regional nodal disease at presentation is relatively uncommon, occurring in 6% to 10% of patients,[31] although up to 16% of patients may experience delayed regional recurrence following treatment.[30] The development of distant metastatic disease occurs in 36% to 77% of patients,[30–32] and the most common site of metastasis is the lungs. Local relapse occurs in 35% to 53% of patients[30–32] and is more common with larger tumor size, tumor location on the scalp, and single-modality treatment.[30,33,34] Local relapse portends a poor prognosis.[30]

Figure 27.1. Angiosarcoma of the right temple **(A)** and scalp **(B)**. Early lesions may mimic that of benign conditions such as bruising, leading to delays in diagnosis.

Angiosarcomas arising in the head and neck have a worse prognosis than do those arising in other sites: the estimated 5-year survival rate for scalp and neck angiosarcomas is 34%, compared to 64% to 75% for those arising at other locations.[35] Among angiosarcomas of the head and neck, angiosarcoma of the scalp is associated with worse disease-specific survival than are tumors at other locations.[30]

The combination of surgery and radiation therapy appears to offer the best chance for local control as well as improved disease-specific and overall survival as compared to either surgery alone or radiation alone.[30,31,33,34] Achieving an R0 resection can be particularly difficult in angiosarcomas of the head and neck given the propensity for a diffuse and multifocal growth pattern.[30,33] Because of this, some have argued against extensive resections

necessitating complicated reconstructions that may delay postoperative radiation therapy.[30] Given the need for adjuvant radiation therapy in nearly all cases of angiosarcoma, repair of surgical defects should be robust enough to withstand radiation therapy. In particular, skin grafting for repair of scalp defects should be avoided when possible. Limited evidence exists to support the role of chemotherapy for localized angiosarcomas, although neoadjuvant taxane-based chemotherapy followed by radiation therapy and/or limited surgical excision has produced encouraging results.[30,36,37]

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EH) is an extremely rare vascular neoplasm with an angiocentric growth pattern and malignant behavior intermediate between that of benign hemangioma and high-grade angiosarcoma. EH occurs most commonly on the extremities but can also occur in the lung, liver, or head and neck.[38] Clinically, EH most commonly presents as a subcutaneous or deep painful nodule. Histologically, EH appears as cords or strands of epithelioid endothelial cells embedded in a matrix that varies from chondroid-like to hyaline-like.[3] Most tumors are low grade, although a small subset displays more aggressive features similar to those of angiosarcomas. There is a tendency for EHs to be misdiagnosed, frequently as metastatic carcinoma.[39,40] EH does have the potential for both regional and distant metastatic spread, which occurs in up to 20% to 30% of cases.[3] Primary treatment is typically surgical resection; adjuvant radiation therapy is used for cases of EH associated with adverse features.

Kaposi Sarcoma

KS is a locally aggressive endothelial cell neoplasm universally associated with human herpesvirus 8 infection. Multiple different subtypes of KS are recognized, including classic, endemic, iatrogenic (immunosuppression associated), and AIDS associated. Of these subtypes, the AIDS-associated subtype is the most frequently found within the head and neck.

KS typically presents with multiple dark brown to violaceous patches that progress to plaques and nodules. Ultimately, these lesions may coalesce and ulcerate. Although the skin is the classic site of involvement, the oral cavity, particularly the hard palate, and the oropharynx are common sites of

involvement in the head and neck.[41,42] Histologically, KS is characterized by irregular proliferation of small blood vessels with an accompanying inflammatory infiltrate and spindled cell proliferation.[3,41]

Treatment for KS differs according to the subtype of KS and extent of disease. Before any specific therapy is undertaken, a thorough evaluation should be performed to assess the full extent of disease. This evaluation should include a head and neck examination as well as ophthalmologic, dermatologic, genital, lymphatic, and radiographic assessments. Any patient in whom the HIV status is uncertain should undergo testing. Therapeutic strategies range from observation in patients with limited asymptomatic lesions to systemic chemotherapy for patients with widespread disease or the endemic subtype. For HIV-associated KS, standard treatment consists of initiation of antiretroviral therapy. In patients with iatrogenic KS, modification of immunosuppressive regimens, including a reduction in the degree of immunosuppression or a change in the drug regimen, may be efficacious. KS is particularly radiosensitive, with high rates of response reported. Patients with head and neck mucosal KS may be particularly susceptible to mucositis from radiation therapy, even at low doses. Radiation therapy is typically reserved for palliation. Surgical excision is typically reserved for symptomatic limited lesions as this therapy is ineffective in preventing the onset of new lesions.[43]

Soft Tissue Tumors of Myocyte Origin

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a soft tissue sarcoma arising from striated muscle. The majority of RMSs occur in children, in whom RMS is the most common soft tissue sarcoma (Table 27.4). However, up to one-third of cases of head and neck RMS are diagnosed in adults.[44] The orbit is involved in one-quarter of cases of RMS; most of the remaining cases arise in the nasopharynx, nasal cavity, and paranasal sinuses.[45] RMS of childhood has been associated with multiple syndromes, including Costello syndrome, Beckwith-Wiedemann syndrome, and Li-Fraumeni syndrome, as well as with neurofibromatosis type 1.[45]

Histologically, RMS appears as a small round blue cell tumor. Three

different histologic subtypes—embryonal, alveolar, and pleomorphic—are recognized and have important prognostic differences. Embryonal RMS is the most common subtype recognized in children and is genetically characterized by loss of heterozygosity at 11p15. Alveolar RMS accounts for ~20% of childhood RMS cases and has a significantly worse prognosis than does embryonal RMS. Two translocations have been well characterized in alveolar RMS: the t(2; 13) (q35; q14) and t(1; 13) (p36; q14) translocations, which result in the *PAX3-FOX01* and *PAX7-FOX01* fusion transcripts, respectively. Survival rates are significantly higher for patients with metastatic tumors harboring the *PAX7-FKHR* fusion transcript than for patients with metastatic tumors harboring the *PAX3-FKHR* fusion transcript; estimated 4-year survival rates are 75% and 8%, respectively.[45] Pleomorphic RMS is more commonly identified in adult-onset RMS than in childhood RMS.[46]

In childhood RMS, regional lymphatic spread is uncommon. Of 139 head and neck RMSs included in Intergroup Rhabdomyosarcoma Study I and II, only 8 (6%) were associated with regional lymphatic spread. For RMSs located within the orbit, there was no demonstrable lymphatic spread, whereas 8% of nonorbital head and neck RMSs demonstrated lymphatic spread.[46] This was considerably lower than the rates of lymphatic spread identified for RMSs of other sites. This low rate of lymphatic spread for head and neck RMSs was confirmed in an analysis of Intergroup RMS Study IV, in which only 9% of pediatric head and neck RMSs demonstrated regional lymphatic spread.[47] In adult RMS, the rate of regional lymphatic involvement is less well defined but appears to be higher than other adult soft tissue sarcomas. In a series of 43 adult patients with head and neck RMS, 18 (42%) had demonstrable involvement of regional lymphatics.[48] Up to 23% of patients with RMS have distant metastatic disease at presentation; therefore, imaging for distant metastases should be part of the workup for all patients with RMS.[2]

For childhood RMS, head and neck tumors are further subdivided into orbital, parameningeal, and nonparameningeal sites. Parameningeal sites include the middle ear, nasal cavity, paranasal sinuses, nasopharynx, pterygopalatine fossa, and infratemporal fossa. Parameningeal RMS accounts for ~40% of cases of pediatric head and neck RMS[45] and is associated with the worst prognosis among RMSs of the head and neck sites because of a

propensity for bony erosion and contiguous intracranial spread and anatomic constraints that limit the application of local therapy.

In general, pleomorphic RMS should be treated similarly to other high-grade soft tissue sarcomas. For embryonal and alveolar RMS, especially cases occurring in pediatric patients, treatment should be performed at a high-volume center.[26] Treatment regimens for nonpleomorphic RMS frequently differ from those for other soft tissue sarcomas. Surgical resection remains an important part of the treatment algorithm. However, given the frequent proximity to critical intracranial structures or extension, complete surgical excision is frequently not achievable without significant morbidity. The Intergroup RMS Study Group and subsequently the Children's Oncology Group Soft Tissue Sarcoma Committee are a tremendous example of the power of cooperative groups to define treatment standards.[49] As example, RMSs in pediatric patients are risk stratified based principally upon surgical and pathologic criteria, and treatment (various combinations of chemotherapy and radiation therapy) is determined by prognostic risk group. Long-term sequelae of radiation therapy in pediatric patients remain significant and can include asymmetric facial growth, cataracts, blindness, cognitive deficits, and radiation-induced secondary malignancies.[2,50]

Overall survival rates have improved significantly following the successes of the Intergroup RMS Studies. For children with head and neck RMS, the 5-year disease-free survival rate ranges from 58% to 74%.[2] Given the rarity of adult RMS, data regarding treatment outcomes are limited, but outcomes in adults are significantly worse than those in younger cohorts.

Leiomyosarcoma

Leiomyosarcoma is a rare soft tissue sarcoma arising from smooth muscle cells. Only a small percentage of leiomyosarcomas are located in the head and neck.[51] Leiomyosarcomas account for ~1% to 14% of head and neck sarcomas[1,17–19,22,52] (Table 27.3). Careful histologic review by an experienced sarcoma pathologist is critical to avoid misdiagnosis, a common occurrence for lesions initially diagnosed as leiomyosarcoma. Additionally, when leiomyosarcoma is suspected, a primary tumor at a more typical abdominal or pelvic site should always be considered and ruled out. The most common locations for leiomyosarcomas in the head and neck are the deep

soft tissues and the skin.[53] Smooth muscle associated with arrector pili muscles and smooth muscles surrounding the vasculature may give rise to leiomyosarcomas.

The mainstay of therapy for leiomyosarcoma is surgical resection with radiation therapy either preoperatively or postoperatively, unless the lesion is superficial. If the lesion is cutaneous and is <2 cm, radiation is typically omitted. Regional and distant spread of disease at presentation is rare, occurring in fewer than 2% of cases.[53] Data are lacking on long-term clinical outcomes of patients with regional or distant spread at presentation. Tumor grade has been identified as an important prognostic factor: 5-year disease-specific survival rates range from 86% to 88% for well and moderately differentiated tumors, compared to 53% for poorly differentiated tumors.[53] Location on the skin has been associated with an improved prognosis.[53]

Soft Tissue Tumors of Fibroblast, Myofibroblast, and So-Called Fibrohistiocytic Origin

Hemangiopericytoma and Solitary Fibrous Tumors

Hemangiopericytomas (HPCs) and solitary fibrous tumors (SFTs) are rare neoplasms thought to arise from pericytes of Zimmerman surrounding small capillaries and postcapillary venules. Historically, HPCs and SFTs were considered separate entities. Now, however, on the basis of overlapping histologic findings and shared molecular alterations, HPCs and SFTs are considered closely related if not synonymous lesions.[3] HPCs/SFTs are composed of varying proportions of fibroblastic spindled cells that stain positive for CD34 and have characteristic sinusoidal or staghorn vasculature, findings that can make differentiation of HPCs/SFTs from synovial sarcoma challenging on the basis of histologic findings alone. Recent advances in molecular characterization of these lesions through whole-genome sequencing have demonstrated that HPCs/SFTs harbor characteristic fusions of the *NAB2* and *STAT6* genes.[54,55]

HPCs/SFTs can occur anywhere in the body. Approximately one-quarter of cases occur within the head and neck, and the sinonasal tract is the most common subsite[2,56] (Table 27.3). HPCs/SFTs of the sinonasal tract most frequently present with epistaxis and nasal obstruction and typically are

located within the nasal cavity and ethmoid sinuses.[56] In other locations, HPCs/SFTs most commonly present as slowly enlarging painless masses.

HPCs/SFTs are locally aggressive. Surgical excision is the standard therapy. Local recurrence occurs in a significant proportion of patients, and the strongest predictor of recurrence is incomplete excision. In a review of more than 190 cases of sinonasal HPCs/SFTs, local recurrence occurred in ~20% of cases with gross total resection, compared to 71% to 100% of cases with incomplete excision.[57] Distant metastatic spread occurs in up to 15% of HPCs/SFTs occurring outside the central nervous system, although distant metastatic spread from tumors located within the head and neck is reported to occur in only 2% of cases.[57] The roles of radiation therapy and chemotherapy for HPCs/SFTs of the head and neck are not well characterized.

Desmoid Tumor/Desmoid Fibromatosis/Aggressive Fibromatosis

Desmoid tumors are monoclonal proliferations of histologically benign-appearing fibroblasts that can occur within deep soft tissues. Clinically, desmoid tumors are characterized by a locally infiltrative growth pattern with high rates of local recurrence but a highly variable clinical course and absence of metastatic potential. The median age at diagnosis has been reported to be in the early fourth decade of life, and the female-to-male ratio of patients with desmoid tumors is ~2:1.[58] Desmoid tumors occur infrequently in the general population; the estimated incidence is 2 to 4 cases per 1 million person-years. Approximately 85% of sporadic desmoid tumors harbor one of three different point mutations in *CTNNB1*, the gene encoding beta-catenin. The *CTNNB1* S45F mutation has been associated with lower recurrence-free survival rates than the *CTNNB1* T41A and S45P mutations.[59] In patients with familial adenomatous polyposis and germline *APC* mutations, desmoid tumors occur in up to 10% of patients.[60] An etiologic role for estrogen in desmoid tumors is suggested by the female preponderance of cases, increased incidence of desmoid tumors in females of reproductive age and during pregnancy, and consistent high expression of estrogen receptor beta in nonabdominal desmoid tumors.[61] A history of trauma at the site of tumor development is also frequently cited[61] but is more likely to have brought the lesion to the patient’s attention than actually to be its cause.

Head and neck desmoid tumors are estimated to account for 7% to 15% of all desmoid tumors.[61] The neck, in particular the supraclavicular fossa, is the most common site of involvement for desmoid tumors of the head and neck.[61] Desmoid tumors most commonly present as enlarging masses. Differentiation from fibrosarcoma, low-grade fibromyxoid sarcoma, and other benign fibrous lesions can be difficult on the basis of histologic findings alone; evaluation for *CTNNB1* mutations can be helpful in such cases.

Treatment for desmoid tumors is an area of controversy. The rarity of desmoid tumors, combined with their highly variable clinical course, which ranges from indolent to locally aggressive and can even include spontaneous resolution, makes evaluation of response to treatment difficult. Historically, surgical resection has been the mainstay of therapy. However, given the infiltrative growth pattern and lack of a well-defined tumor capsule, R0 resections are difficult, particularly in the head and neck, where proximity to critical structures frequently limits the width of surgical resection margins.[62,63] Given the variable clinical course and difficulty of achieving negative margins, most authors agree that mutilating surgery should be avoided. For patients without a history of rapid growth or proximity of tumor to critical structures, a period of observation may be considered. For desmoid tumors of the abdominal wall, high rates of spontaneous regression have been reported with a strategy of initial observation.[64] Radiation therapy can achieve disease stabilization and prevent progression[65] and in some cases shrinks the tumor. The potential benefits of radiation therapy should be balanced against long-term side effects on an individualized basis.[66,67] No standardized systemic therapy paradigm has emerged. Regimens used to date have included traditional cytotoxic therapies, nonsteroidal anti-inflammatories, tamoxifen, and imatinib.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a rare low-grade cutaneous sarcoma of fibroblast origin with little metastatic potential. DFSP accounts for 4% of soft tissue sarcomas and 4% to 10% of head and neck sarcomas.[2] The incidence is approximately four cases per million person-years, and the median age at diagnosis is in the fourth decade of life.[2]

DFSP is characterized by an indolent clinical course but an infiltrative growth pattern with irregular subclinical tumor extensions. The most common site of involvement is the scalp (Table 27.3), where DFSPs most commonly appear as painless raised nodules or plaques, a fact that may lead to delayed diagnosis. Surgical excision with histologically negative margins is the treatment of choice for DFSP when possible. High rates of local recurrence are noted with incomplete surgical excisions and with positive initial resection margins, so re-excision should be attempted in such cases when not prohibited by proximity of the tumor to critical structures.[26] When re-excision is not possible or when complete surgical excision would be associated with unacceptable adverse effects, adjuvant radiation therapy combined with conservative surgical excision affords high rates of local control.[68]

A characteristic chromosomal translocation—t(17;22), resulting in fusion of the *COL1A1* and *PDGFβ* genes—occurs in DFSP, resulting in activation of the platelet-derived growth factor receptor beta (PDGFβ) signaling pathway.[69] Imatinib, a tyrosine kinase inhibitor with activity against PDGFβ, has emerged as an alternative adjuvant therapy for patients with metastatic or inoperable DFSP, and complete and partial response rates to this day range from 36% to 57%.[70,71]

Local recurrence occurs in 1% to 60% of patients with DFSP and may be quite delayed.[72,73] Distant metastatic disease ultimately occurs in 2% to 4% of patients.[72,73] In patients who have surgical excision with negative margins, estimated 5-year overall survival rates are excellent, approaching 100%.[2]

MFH/Undifferentiated High-Grade Pleomorphic Sarcoma

Historically, MFH was considered a discrete soft tissue sarcoma with a suspected fibroblastic origin that displayed both fibrous and histiocytic differentiation. More recently, it has been recognized that the histologic pattern of MFH may be shared by a wide variety of poorly differentiated neoplasms. Consequently, the term *malignant fibrous histiocytoma* is now reserved for soft tissue malignancies for which no reliable line of differentiation may be established, and MFH is considered synonymous with undifferentiated high-grade pleomorphic soft tissue sarcoma. In historic

series, MFH represented the most common soft tissue sarcoma in adults and one of the most frequent soft tissue sarcomas of the head and neck.[1,11,74]

MFH typically occurs in the fourth to sixth decades of life and is rarely identified in young patients. The vast majority of MFH lesions arise spontaneously; however, in the rare patient who develops a radiation-associated sarcoma after previous radiation therapy, the histology is often MFH or undifferentiated pleomorphic sarcoma.[74] In a series of over 2,000 long-term survivors of nasopharyngeal carcinoma who were treated with radiation therapy, the prevalence of MFH was 0.4%, and the 15-year cumulative incidence was 2%.[75] MFH most commonly presents as a mass. The most common sites of involvement are the parotid and neck, followed by the scalp, face, and then the anterior skull base and orbit; less commonly involved are the aerodigestive tract and lateral skull base[75] (Tables 27.3 and 27.4). Specific symptoms depend on the tumor location. Involvement of regional lymphatics is infrequent, although distant spread, most frequently to the lungs, has been reported in up to 16% of patients.[74]

The management of MFH requires a true multidisciplinary approach. While the primary treatment modality remains surgical excision, high rates of positive margins and frequent local recurrence necessitate the use of adjuvant radiation therapy either before or after surgery in a majority of patients. However, if the patient has a radiation-associated sarcoma, reirradiation is not recommended due to morbidity concerns associated with reirradiation. Because patients with undifferentiated high-grade pleomorphic sarcomas are at increased risk for distant metastatic spread, the use of neoadjuvant or adjuvant chemotherapy should routinely be considered.

Although population-level data are not available for head and neck MFH, estimated survival rates are available from a large series of patients with MFH of the head and neck, in which 5-year overall, disease-specific, and disease-free survival rates were estimated to be in the range of 55%, 69%, and 44%, respectively.[74] Factors associated with a poor prognosis in patients with MFH include positive surgical margins, tumor size >5 cm, high grade, location other than in the parotid or neck, and tumor arising in a previously irradiated field.[74,76–78]

Fibrosarcoma

Fibrosarcomas are malignant neoplasms of fibroblastic or myofibroblastic origin. Historically, fibrosarcoma was one of the most frequent soft tissue sarcomas identified. However, with advances in immunohistochemistry and molecular diagnosis, many lesions previously classified as fibrosarcomas are now recognized to be of different histologic subtypes.[79,80] Reclassification of lesions in historic series of head and neck fibrosarcomas has demonstrated that the majority of lesions reported to be fibrosarcomas would now be classified as desmoid tumors, dermatofibrosarcomas, synovial sarcomas, and MFH/pleomorphic undifferentiated high-grade sarcomas.[79] Advances in immunohistochemistry and molecular diagnosis have also led to the recognition of multiple new subtypes of fibrosarcomas, including myxofibrosarcoma, low-grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma, and the classic adult fibrosarcoma, which is now a diagnosis of exclusion.[3]

Adult fibrosarcoma is a malignancy of fibroblast origin with variable collagen production. Classic adult fibrosarcoma appears as sweeping fascicles of spindle-shaped cells in a herringbone pattern.[3] Limited data are available on incidence rates, optimal treatment, or clinical outcomes for adult fibrosarcomas diagnosed using modern diagnostic criteria.

Myxofibrosarcomas are malignant neoplasms of fibroblast origin characterized histologically by myxoid stroma and a characteristic curvilinear vascular pattern.[3] They are most commonly located on the extremities but rarely occur in the head and neck. Myxofibrosarcomas have a high propensity for local recurrence regardless of tumor grade; recurrence rates of 50% or higher have been reported.[81,82] Regional lymph node spread occurs in ~8% of cases,[82] and distant metastasis, most commonly to the lungs, occurs in ~15% of cases.[81,82]

Low-grade fibromyxoid sarcoma and sclerosing epithelioid fibrosarcoma are very rare subtypes of fibrosarcoma, and only a few cases of these tumors occurring in the head and neck have been reported in the literature. Low-grade fibromyxoid sarcoma is characterized by bland-appearing spindled cells with rare mitoses admixed with heavily collagenized zones and a whorling growth pattern. Up to 40% of cases demonstrate poorly formed collagen rosettes.[3] It has been reported that 81% to 88% of low-grade fibromyxoid sarcomas harbor a characteristic translocation of either the *FUS*-

CREB3L2 or *FUS-CREB3L1* fusion.[83,84] Despite the bland histologic appearance, up to 64% of patients with low-grade fibromyxoid sarcoma develop local recurrence, and 21% to 45% develop metastatic disease.[83,84] In contrast to what is observed with many soft tissue sarcomas, both local recurrence and metastasis of low-grade fibromyxoid sarcoma can occur many years after diagnosis, which highlights the need for lifelong follow-up in these patients.[84,85] Sclerosing epithelioid fibrosarcoma is characterized by nests of epithelioid cells embedded in a sclerotic collagenous matrix. *EWSR1-CREB3L1* fusions have been identified in a moderate proportion of cases.[86] High rates of local recurrence (50% to 53%) and distant metastasis (43% to 86%) have been noted.[87,88]

Soft Tissue Tumors of Adipocyte Origin (Liposarcoma)

Liposarcomas are soft tissue sarcomas arising from adipocyte precursors. Liposarcomas are most frequently found in the deep soft tissues of the extremities and retroperitoneum; only 2% to 9% of liposarcomas are localized to the head and neck.[89] Liposarcomas account for ~2% to 4% of all head and neck sarcomas[1,11,19] (Table 27.3). There is a male preponderance (77%) for head and neck liposarcomas, which differs from the more even gender distribution (58% male) for liposarcomas located in other anatomic regions.[89] The majority of head and neck liposarcomas are located in the subcutaneous tissues of the head and neck; involvement of the skin, aerodigestive tract, or major salivary glands is less common.[89,90]

Compared with liposarcomas at other anatomic sites, liposarcomas of the head and neck are more likely to present at an early stage and higher degree of differentiation. Up to 89% of head and neck liposarcomas present as stage I or II, and an estimated 70% are well differentiated.[89] A number of different histologic subtypes are recognized by the WHO, including well-differentiated, dedifferentiated, myxoid, round cell, pleomorphic, and mixed-type liposarcomas. Within the head and neck, well-differentiated liposarcomas (WDLs) account for 23% to 45% of all liposarcomas, myxoid subtype for 36%, pleomorphic subtype for 10%, and dedifferentiated subtype for 7%. The remaining subtypes are rare.[89–91]

Atypical lipomatous tumor (ALT) and WDL are now recognized as identical entities with similar morphologic and karyotypic characteristics and

similar nonmetastasizing but locally aggressive clinical behavior. These entities most often present as painlessly enlarging masses.[90] ALT/WDL is characterized histologically by the presence of mature adipocytes. Genetically, supernumerary ring and giant rod chromosomes are noted, as well as amplification of 12q14-15, the region encoding *MDM2*.[3] Although ALT/WDLs are not associated with significant rates of regional or distant spread, local recurrence remains a significant problem, occurring in up to 43% of cases.[90] When regional or distant metastatic spread does occur, it is associated with dedifferentiation.

Dedifferentiated liposarcoma is an undifferentiated sarcoma with various histologic features arising from an ALT/WDL. Dedifferentiated liposarcomas are associated with molecular alterations similar to those in ALT/WDL.[26] It has been reported that up to 10% of WDLs may undergo dedifferentiation, although no rate of dedifferentiation has been reported specifically for lesions arising solely within the head and neck.[3] Along with loss of differentiation comes a risk for distant metastatic spread, which occurs in 15% to 20% of cases.[3] Like ALT/WDL, dedifferentiated liposarcoma is associated with a high rate of local recurrence.

Myxoid liposarcoma and round cell liposarcoma are synonymous histologic subtypes of liposarcoma that are characterized histologically by round or oval mesenchymal cells and small signet ring lipoblasts within a myxoid stroma.[3] These tumors most frequently occur in the lower extremities, although myxoid liposarcoma is also the second most frequent histologic subtype of liposarcoma occurring in the head and neck, accounting for one-third of all head and neck liposarcomas.[89] Like ALT/WDL, myxoid liposarcomas tend to be well differentiated. Myxoid liposarcomas are characterized by the t(12;16)(q13;p11) translocation, which is present in more than 95% of cases.[92] Myxoid liposarcomas have a peak incidence in the fourth and fifth decades, which is a decade earlier than for other liposarcoma subtypes.[3] Distant metastatic spread from myxoid liposarcomas predominantly occurs at extrapulmonary sites, and there is a high predilection for metastasis to the spine.[93–95] A higher rate of distant metastatic spread and worse survival has been noted for tumors with round cell morphology.[90,93]

Pleomorphic liposarcoma is a high-grade liposarcoma characterized by the presence of pleomorphic lipoblasts. Clinically, pleomorphic sarcoma

differs from other liposarcoma histologic subtypes in that it has an aggressive clinical course characterized by a high propensity for distant metastatic spread and poor overall prognosis.[89,96] Pleomorphic liposarcomas account for ~10% of all head and neck liposarcomas. Distant metastatic spread occurs in up to 35% of cases, and the most common site of metastasis is the lungs.[96]

The preferred treatment for all histologic subtypes of liposarcoma is complete surgical resection with negative margins. However, given the proximity of critical neurovascular structures in the head and neck, this is frequently impossible. Evaluation by a radiation oncologist and head and neck surgeon experienced in the management of these tumors is preferred in determining the best local management approach for these complex tumors. In general, liposarcomas are considered to be chemotherapy-resistant tumors, though myxoid liposarcomas have been demonstrated to be sensitive to trabectedin, an agent that targets the nucleotide excision repair machinery.[97,98]

Disease-specific and overall survival has been reported to be better for head and neck liposarcomas than for liposarcomas at other anatomic locations. In large part, this difference appears to be driven by a higher proportion of patients presenting with well-differentiated histologic subtypes and early-stage disease.[89] Five-year disease-specific survival rates for patients with head and neck liposarcomas range from 73% to >90%, and 5-year overall survival rates range from 66% to 80%.[89,90] Histologic subtype and grade both appear to influence survival outcomes. Disease-specific and overall survival have been reported to be lower for pleomorphic liposarcoma than for other subtypes, and dedifferentiated liposarcoma has been demonstrated to have lower overall survival rates than ALT/WDL and myxoid histologic subtypes.[89]

Soft Tissue Sarcomas of Neurogenic Origin

Malignant peripheral nerve sheath tumor (MPNST), also known as neurogenic sarcoma, neurofibrosarcoma, and malignant schwannoma, is a rare sarcoma arising from peripheral nerves. MPNSTs occur in young patients: the median age at diagnosis is ~35 years.[99] Risk factors for the development of MPNST include a history of prior exposure to radiation and neurofibromatosis type I. The lifetime risk of developing an MPNST in a

patient with neurofibromatosis type I has been estimated to be 8% to 13%.[100] In neurofibromatosis type I, MPNSTs have been noted to frequently arise from preexisting neurofibromas.

Approximately 15% of MPNSTs occur in the head and neck,[100] most commonly in the neck (Tables 27.3 and 27.4). MPNSTs are high-grade, aggressive neoplasms with a predilection for local recurrence and a potential for distant metastatic spread. A small percentage of tumors demonstrate regions of rhabdomyoblastic differentiation and are termed "triton" tumors. Surgical resection is the treatment of choice. The benefits of adjuvant radiation therapy and chemotherapy are not well characterized.

Soft Tissue Sarcomas of Unclear Histologic Origin

Synovial Sarcoma

Synovial sarcoma is a spindle cell mesenchymal malignancy with varying degrees of epithelial differentiation that carries the specific chromosomal translocation t(X;18)(p11;q11). Misdiagnoses for this entity have included carcinosarcoma and spindle cell carcinoma, which highlights the variable epithelial differentiation of this tumor. Synovial sarcomas typically present as slowly growing lesions and may be present for many years before diagnosis. Histologically, they may demonstrate either a monophasic or biphasic growth pattern. Synovial sarcomas may present at any age, although the median age at presentation for head and neck synovial sarcomas is in the third decade of life. There appears to be a slight male preponderance in most series.[101] Within the head and neck, there appears to be a predilection for the paraspinous part of the neck[101,102] (Table 27.3).

Reported rates of local recurrence range from 32% to 62%, and reported rates of distant metastatic spread range from 33% to 48%; however, regional disease is rare, with reported rates ranging from 0% to 14%.[101–103] In the largest series published to date, overall and disease-specific survival rates at 5 years were 72%.[101] Tumor size larger than 5 cm, positive margins, and skull base location have all been associated with a worse prognosis.[101–103] As with other sarcomas, surgical resection with negative margins remains the gold standard. Patients treated with adjuvant radiation therapy have superior outcomes, and use of radiation therapy in addition to surgical excision should

be routinely considered.[101] The use of adjuvant chemotherapy remains controversial, but many authors favor neoadjuvant chemotherapy because of the high risk of distant metastases and because responses to neoadjuvant chemotherapy are generally good, which can facilitate local therapies.

Alveolar Soft Part Sarcoma

ASPS is a rare soft tissue sarcoma accounting for fewer than 1% of head and neck soft tissue sarcomas (Table 27.3). Histologically, ASPS is characterized by nests of large uniform epithelioid cells separated by delicate septations with sinusoidal vascular channels. Although ASPS is most frequently found in the extremities, ASPS occurring in children frequently involves the orbit and tongue.[3,104] A gender ratio inversion—a female preponderance in young patients transitioning to a male preponderance in patients presenting later in life—has been noted.[3,105] ASPS is a highly vascular tumor with high signal intensity on T1 and T2 magnetic resonance imaging and significant enhancement on contrast-enhanced computed tomography. Clinically, ASPS is characterized by an indolent local growth pattern and low rate of local relapse following surgical resection. Despite this, distant metastatic spread is found on presentation in up to 65% of patients.[105,106] Most commonly, this involves the lungs and bones. Patients with lung metastases are also at significant risk for developing intracranial metastatic disease.[105] Brain imaging should be performed in patients with symptoms suggestive of intracranial metastatic disease or in those who have known pulmonary metastases.[105]

For ASPS, as for other sarcomas, surgical resection is the mainstay of therapy when distant metastatic disease is not present. Limited responses to doxorubicin-based, ifosfamide-based, and cisplatin-based chemotherapy regimens have been noted.[105,106] Given the high rates of local control in most series, adjuvant irradiation of the primary tumor site may not be necessary for cases in which wide negative margins can be achieved. Localized ASPS is associated with favorable long-term outcomes: a 5-year disease-free survival rate of 71% and overall survival rates of 60% to 88% have been reported.[105–107] Although limited reports of patients with head and neck ASPS preclude meaningful comparisons between ASPS of the head and neck and ASPS of other anatomic sites, there has been the suggestion of a lower

rate of distant metastatic spread and improved prognosis for tumors at head and neck sites.[108]

CARTILAGINOUS AND BONY SARCOMAS

Osteosarcoma

Osteosarcoma is the most common primary bone malignancy. Osteosarcomas of the head and neck represent a minority of all osteosarcomas, accounting for only an estimated 10% of all cases.[109,110] The median age at diagnosis for head and neck osteosarcomas is in the fourth decade of life, which is later than the median age at diagnosis for osteosarcomas of other anatomic locations.[110] A number of risk factors for the development of osteosarcoma have been reported, including Paget disease; hereditary retinoblastoma; Werner, Rothmund-Thomson, and Li-Fraumeni syndromes; and a history of prior radiation exposure. Histologic subtypes of conventional osteosarcoma (osteoblastic, chondroblastic, and fibroblastic subtypes) account for the vast majority of reported cases.[110] In a review of 496 cases in the National Cancer Data Base, osteoblastic osteosarcoma accounted for 77% of all cases and chondroblastic osteosarcoma for 16%.[110] The mandible and maxilla are overwhelmingly the most frequently involved sites, accounting for 39% to 56% and 32% to 45% of cases, respectively.[109–112] A classic radiographic appearance is of a mandibular lesion with a “sunburst” pattern (**Fig. 27.2**). From 50% to 63% of all head and neck osteosarcomas are classified as high-grade tumors.[109–112]

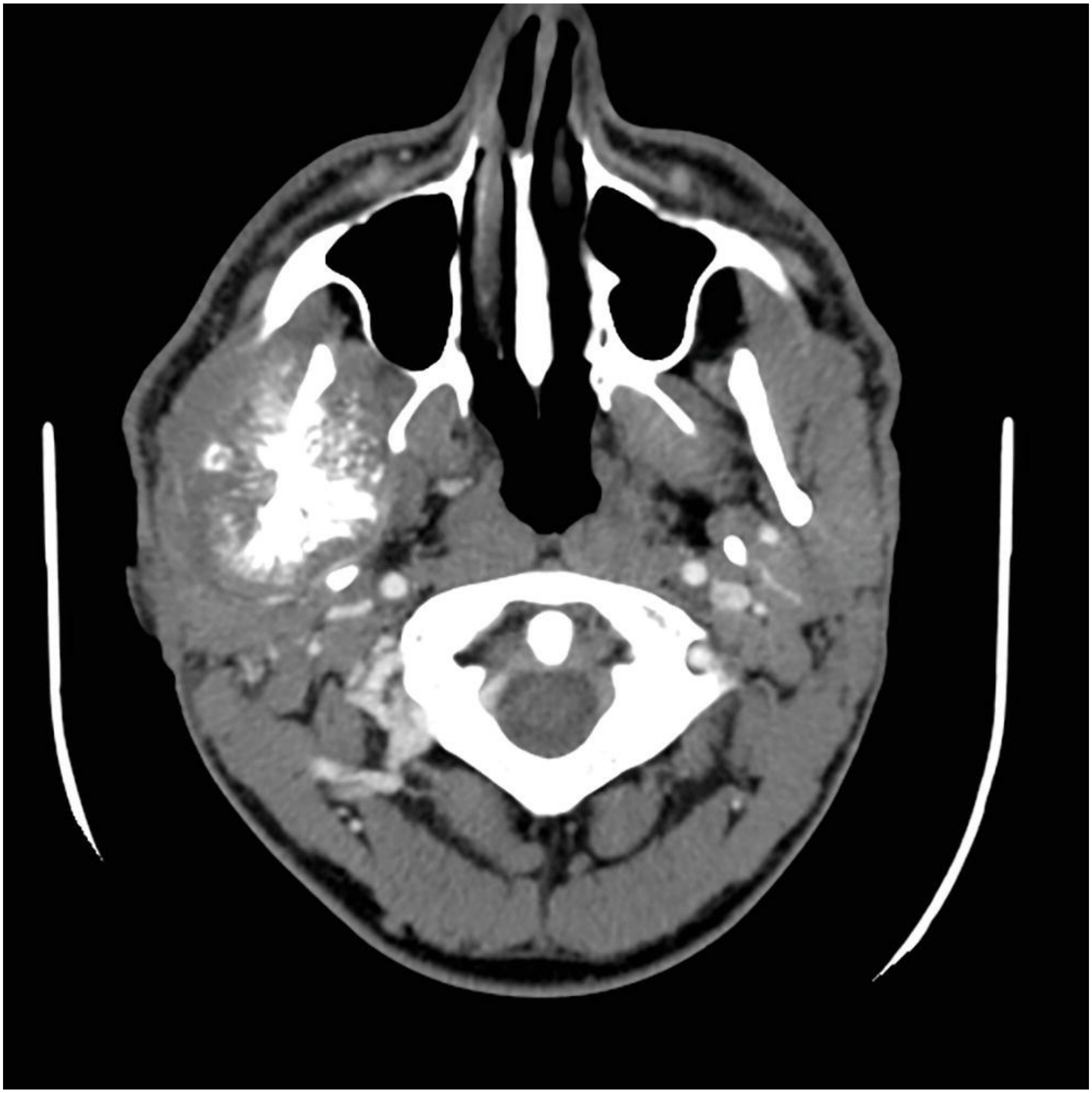

Figure 27.2. Osteosarcoma of the mandible with characteristic "sunburst" radiographic pattern.

The primary treatment for osteosarcoma is surgical resection; use of adjuvant chemotherapy and radiation therapy is dictated in large part by tumor grade, preoperative resectability, soft tissue extension, and postoperative or anticipated margin status in addition to the patient's ability to tolerate therapy. Surgical margin status and tumor grade are consistently reported as the most important prognostic factors in osteosarcoma. Patients with negative margins have reported 5-year survival estimates of 75%,

compared to 32% for those with residual disease following surgery.[110] Similar 5-year survival differences have been noted between patients with high-grade tumors (42%) and low-grade tumors (74%). Adjuvant radiation therapy has been demonstrated to improve local control and survival in patients with positive margins.[109] The role of adjuvant chemotherapy remains less well defined for head and neck osteosarcomas than for osteosarcomas at other anatomic locations. Head and neck osteosarcomas have been demonstrated to have lower rates of distant metastatic spread (4% to 29%) and high rates of local recurrence (20% to 63%).[109,111–113] Current evidence suggests that incorporation of adjuvant (often neoadjuvant) chemotherapy is warranted in high-risk cases.[110,113] Across all stages, histologic subtypes, and anatomic sites, 5-year disease-free and disease-specific survival estimates range from 49% to 70%, and 5-year disease-specific survival estimates range from 60% to 75%.[109,110,112,113]

Chondrosarcoma

Chondrosarcomas are thought to arise from cartilaginous cells that characteristically produce a chondroid matrix. Several histologic variants are recognized, including classic chondrosarcoma and periosteal, dedifferentiated, mesenchymal, and clear-cell subtypes. Both classic and periosteal chondrosarcomas are malignancies with a pure hyaline cartilage differentiation; the periosteal variant occurs in a juxtacortical location. The dedifferentiated, mesenchymal, and clear-cell variants are rarely reported in the head and neck.

Overall, chondrosarcomas of the head and neck are rare and account for ~5% of all chondrosarcomas.[114] Within the head and neck, the most common site of involvement is the bones of the head and neck, including the skull base and sinonasal tract, where 60% of cases arise, and the larynx, where 23% of cases arise; the remainder of cases occur in soft tissues of the head and neck and other miscellaneous sites.[115] The vast majority of chondrosarcomas of the head and neck (88%) are well or moderately differentiated, and regional disease and distant disease are rare (occurring in 6% and 7% of cases, respectively).[115]

Laryngeal chondrosarcomas are incredibly rare, accounting for only 0.2% of all laryngeal malignancies.[116] Laryngeal chondrosarcomas demonstrate a

predilection for whites, and the male-to-female ratio has been reported to be 3:1. The median age at diagnosis is 62 years.[116] In a series of 111 cases from the Air Forces Institute of Pathology, the vast majority of laryngeal chondrosarcomas were noted to occur in the cricoid (77% of cases) and thyroid cartilages (19%).[117] High-grade laryngeal chondrosarcomas are rare; 95% of chondrosarcomas are of low or moderate grade.[117] In two large series, regional lymph node involvement was not noted, and distant metastatic disease occurred in only 2% of cases.[116,117] Laryngeal chondrosarcomas typically present with local symptoms of dysphagia, voice changes, and dyspnea.[117] They have a pathognomonic appearance on computed tomography of calcified mass with a stippled appearance within a distorted and enlarged cartilage, most typically of the posterior table of the cricoid (**Fig. 27.3**). The recommended treatment is surgical excision. Given the low rates of regional and distant metastatic spread and the favorable grade of the majority of tumors, many authors advocate a laryngeal conservation approach to the initial treatment of laryngeal chondrosarcomas,[118] although this remains an area of controversy. Variable sensitivity to radiation therapy has been reported in the literature, but adjuvant radiation therapy tends to be reserved for high-risk lesions, such as high-grade tumors, tumors with positive margins, and/or tumors of the skull base. Local recurrence occurs in up to 18% of patients.[116,117] Despite this, long-term disease-specific survival remains good, highlighting the ability to successfully treat recurrences.

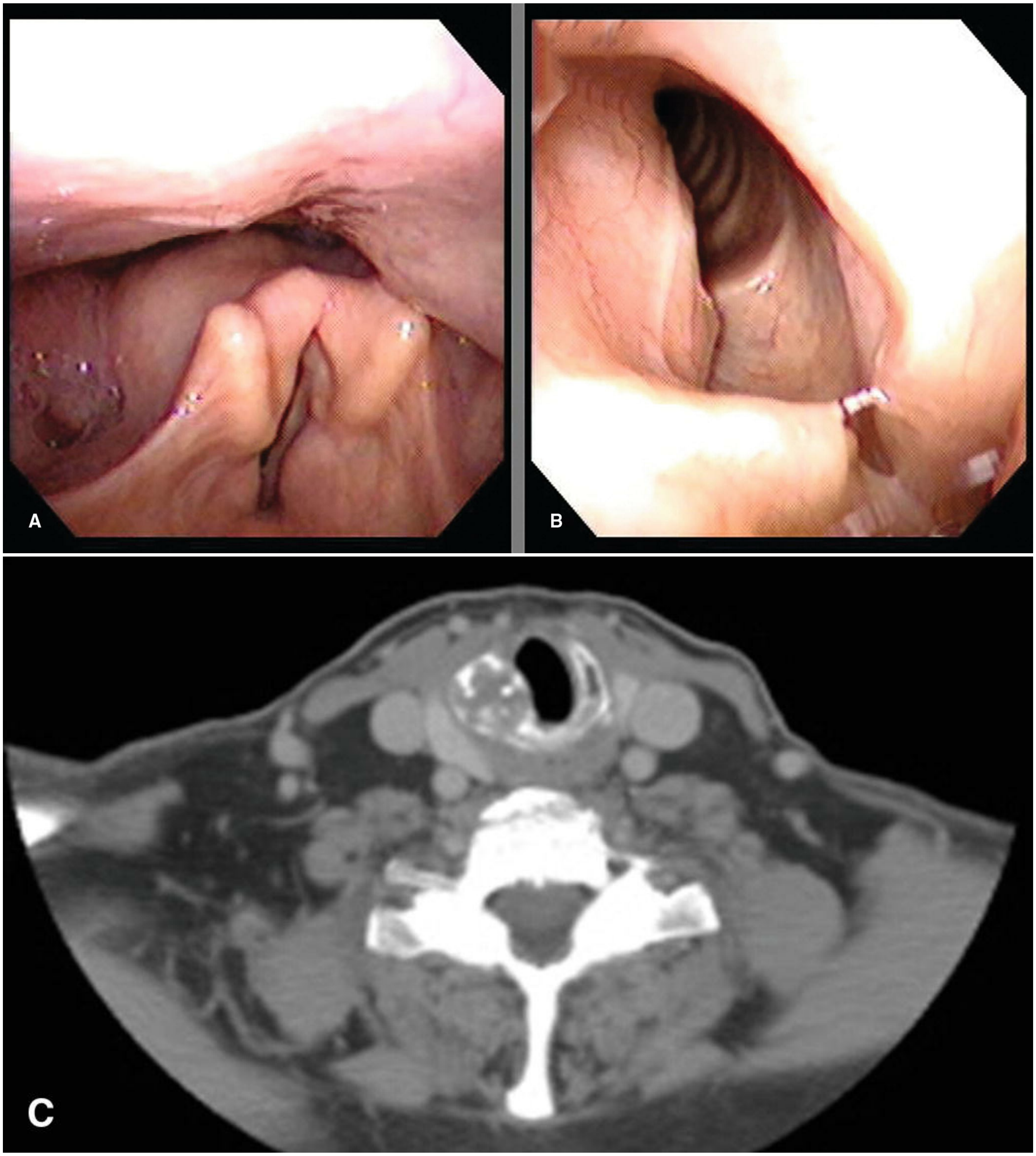

Figure 27.3. Chondrosarcoma of the cricoid cartilage **(A)** Submucosal mass arising from the posterolateral cricoid, **(B)** Intraluminal extent of chondrosarcoma visualized inferior to the right vocal cord, **(C)** computed tomography scan demonstrating the classic appearance of an expansile radiolucent mass with punctate calcification.

Chondrosarcomas of the skull base occur most commonly in the

petroclival synchondrosis, followed by the clivus; less common locations are the sphenoid and ethmoid sinuses.[119] As with laryngeal chondrosarcomas, high-grade lesions are rare, and the conventional chondrosarcomas histologic subtype predominates.[119] A unique diagnostic challenge for skull base chondrosarcomas is differentiation from chordomas, particularly for tumors with myxoid stromal.[119] Given the proximity to critical neurovascular structures, en bloc resection with negative margins is rarely achievable. Although radiation therapy for chondrosarcomas in other anatomic locations is controversial,[117] use of primary radiation therapy or adjuvant radiation therapy following partial resection is well accepted for skull base chondosarcomas.[118,119] In a systematic review of 560 patients with chondrosarcomas of the skull base, patients treated with surgery alone had a 5-year recurrence rate of 44%, compared to 19% for patients treated with definitive radiation therapy and 9% for patients treated with both surgery and radiation,[120] suggesting that surgery may have a role even when complete surgical resection is not possible. Although the best type of radiation therapy remains controversial, most authors agree that a highly conformal technique and high radiation dose to overcome intrinsic tumor radioresistance are critical components of radiation therapy for skull base chondrosarcomas.[121]

In general, treatment for head and neck chondrosarcomas consists of surgical excision with negative margins if possible. For high-grade lesions, tumors with positive margins, and tumors at the skull base, adjuvant radiation therapy is warranted. Local recurrence remains a concern even in low-grade lesions. Population-based estimates suggest 5- and 10-year disease-specific survival rates to be 87% to 89% and 71% to 85%, respectively.[115,116]

Ewing Sarcoma/Primitive Neuroectodermal Tumor

Ewing sarcoma and primitive neuroectodermal tumor (PNET) are small round blue cell tumors that display varying degree of neuroectodermal origin. Although these tumors were originally considered separate entities because of limited histologic evidence of neuroectodermal origin in classic Ewing sarcoma, progress in molecular classification has demonstrated that Ewing sarcoma/PNET tumor have similar cytogenic findings and should be considered in the same family of malignancies. A t(11;22)(q24;q12) translocation is present in 90% of cases, and a similar translocation, t(21;22)

(q22;q12), accounts for the remaining cases.[122] In both subsets, the translocation results in fusion of the *EWSR1* gene to an ETS gene, with the resultant chimeric protein acting as a transcription factor for ETS target genes.

Ewing sarcoma PNET tumor overwhelmingly occurs in childhood; the median age at presentation is in the second decade of life. Ewing sarcoma/PNET tumor is the second most common bony malignancy in children, after osteosarcoma, and typically involves the long bones, pelvis, and ribs. It is rare in the head and neck; head and neck tumors account for only 15% to 4% of all cases.[123] The mandible, skull, and maxilla are frequent sites of involvement for Ewing sarcoma/PNET of the head and neck, although this disease can also occur at soft tissue sites.[124–126] Regional node involvement is rare in Ewing sarcoma/PNET, but distant metastatic spread is present in 13% to 19% of patients at presentation, and up to an additional 45% of patients develop distant metastatic spread later.[124,127]

Similar to RMS, Ewing sarcoma/PNET is sensitive to chemotherapy and radiation therapy. Treatment parallels treatment for RMS, in which use of systemic neoadjuvant multiagent chemotherapy is standard. When wide local resection with negative margins is possible, this is preferred if the morbidity of surgery is not anticipated to be excessive. When negative-margin surgery is not possible or surgery is expected to be mutilating, which is often the case for Ewing sarcoma/PNET of the head and neck, radiation therapy should be used. Local recurrence occurs in up to 29% of cases.[124] Ten-year overall and disease-free survival estimates range from 63% to 66% and 52% to 56%,[126,127] respectively.

SUMMARY

Sarcomas arising within the head and neck can be challenging to treat and require an experienced multidisciplinary team to achieve the best outcomes. The goal of achieving local control must be balanced with the need to address the risk of distant metastatic disease, which is a major concern with many sarcoma histologic subtypes. Frequently, patients require multidisciplinary treatment consisting of a combination of systemic and local therapies. For most sarcomas, complete surgical resection is the cornerstone of local therapy. Given the frequent proximity of head and neck sarcomas to vital

structures in the region, complete resection can be challenging. For most sarcomas arising in the head and neck region, preoperative or postoperative radiation therapy is generally indicated to optimize local control, and preoperative irradiation has advantages over postoperative irradiation in many situations. For histologic subtypes with high rates of distant metastatic spread, adjuvant (typically neoadjuvant) systemic chemotherapy is often incorporated into the treatment regimen. As our knowledge of the molecular underpinnings of sarcoma continues to evolve at a rapid pace and as new targeted therapies are developed on the basis of these new insights, it is hoped that outcomes of treatment for sarcoma will continue to improve.

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28 Reconstruction of Major Defects in the Head and Neck Following Cancer Surgery

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Contemporary surgical management of cancer of the head and neck is the product of the continued application of new oncologic and reconstructive techniques. Patient survival and functional rehabilitation have improved since the mid-1940s, before which orthovoltage radiation was the mainstay of treatment of cancer of the head and neck. With the introduction of modern techniques of anesthesia, antibiotics, blood banking, and new techniques of radical surgery, wide resection of primary cancers of the upper aerodigestive tract and incontinuity neck dissection of regional metastases has resulted in improved cure rates. Thereafter, advances in radiation therapy led to the introduction of “combined therapy.” As an accepted trade-off for improved survival rates, this aggressive approach often resulted in prolonged hospitalization, major functional and cosmetic deficits, and, in many cases, social isolation, as well as the inability to maintain gainful employment.

The development of reconstructive techniques for head and neck surgery did not progress at the same pace as combined therapy for eradication of cancer of the head and neck. In fact, most authors either failed to acknowledge the issue of reconstruction or deemed it unnecessary. Hayes Martin,[1] the father of modern head and neck surgery, wrote:

> “Excessive or too frequent resort[ing] to more complicated and technical procedures,

> such as skin graft for pharyngeal defects, skin graft of the tongue or buccal surface, … bone grafts in mandibular defects, and particularly nerve grafts for [seventh cranial] nerve defects, is not characteristic of the mature or resourceful surgeon."

Before 1963, most oral and pharyngeal defects were closed primarily, reconstructed with random-pattern skin flaps (such as the nape of neck flap), or reconstructed with tubed, pedicled flaps of skin from the trunk. These flaps rarely matched the tissue requirements of the defect. Furthermore, such repairs were unpredictable and frequently resulted in flap necrosis, salivary fistula, bone or carotid artery exposure, or other complications that led to prolonged hospitalization or the patient's death.

The previously limited ability of surgeons to resurface mucosal defects of the head and neck improved with the description of the forehead flap by McGregor[2] in 1963 and the deltopectoral flap by Bakamjian[3] in 1965. These well-vascularized, axial-pattern skin flaps permitted more reliable closure of oral and pharyngeal defects at the time of ablative surgery. Although these reconstructive techniques permitted extensive resection to be performed more safely, their limitations soon became apparent. The limited arc of rotation frequently necessitated multistaged, delayed procedures and prolonged hospitalization. The need to perform skin grafts for all but the smallest donor defects contributed to suboptimal aesthetic results. Furthermore, the limitations of the transferred tissue in restoration of function frequently led to permanent impairment of deglutition, articulation, and mastication. Despite their drawbacks, the forehead and deltopectoral flaps were the mainstays of soft tissue reconstruction of head and neck defects for nearly two decades.

The rehabilitation of patients with cancer of the head and neck has been revolutionized since the mid-1970s by the development of advanced reconstructive techniques. Pedicled myocutaneous flaps and free tissue transfers have allowed reliable and safe one-stage primary reconstruction of defects of the upper aerodigestive tract. In the late 1970s and early 1980s, the pedicled pectoralis major myocutaneous flap was popularized and became the predominant method used in reconstruction of the head and neck. Other regional flaps, such as the trapezius and latissimus dorsi flaps, were described for reconstruction of defects of the head and neck region. As clinical experience accumulated, the limitations of pedicled flaps for some reconstructive problems became apparent. These include the limited lengths of the pedicle with restriction of the arcs of rotation, excessive bulk, and

donor site morbidities. In addition, the inability of surgeons to reliably transfer vascularized bone for mandibular reconstruction stimulated the search for alternative techniques.

A new approach to transferring tissue became available in 1973 with the advent of microvascular surgery. Subsequently, free tissue transfer rapidly evolved from a reconstructive “last resort” into the preferred method of addressing a variety of complex defects of the head and neck. As new donor sites were discovered and microsurgical techniques were refined, the advantages of free tissue transfer for certain reconstructive problems became apparent. These advantages include the following: (1) superior vascularity of the tissues, resulting in improved tissue survival and wound healing in unfavorable recipient beds; (2) freedom from a limited arc of rotation and length of the vascular pedicle; (3) greater availability, variety, and versatility of donor tissue; and (4) presence of donor sites that are less morbid and conspicuous.

Surgeons are now able to perform more extensive resections with the comfort and confidence of knowing that the available reconstructive procedures can successfully repair the defect in the primary setting and provide the cancer patient with the best opportunity for a rapid functional and cosmetic rehabilitation, as well as prompt initiation of postoperative adjuvant treatments. A good example of the interplay between reconstructive and ablative surgery is seen in cases affecting the region of the cranial base, where vital structures such as the brain and carotid artery can now be reliably covered and protected with well-vascularized tissue. The ability to separate the cranial cavity from the sinonasal tract has been critical to the advancement of the emerging discipline of cranial base surgery. Despite longer and more technically demanding procedures, the success rate of microvascular free tissue transfers to the head and neck region has continued to improve, approaching 98% and 99%.[4,5] Consequently, free tissue transfer has become an essential part of the comprehensive management of many surgical defects in the head and neck.

This chapter presents our approach to the various problems of reconstruction of defects in the head and neck. Available techniques, indications for clinical application, and functional and aesthetic issues are discussed. Although skin grafts and local flaps are effective for the resurfacing of small mucosal and cutaneous defects, reconstruction of larger

defects usually requires transfer of tissue from regional or distant sites. This chapter addresses the latter techniques and also describes the contemporary approach to achieve functional dental restoration. Finally, an approach to the functional assessment of the head and neck cancer patient will be presented in order to provide a framework for assessing the outcomes of surgery and adjuvant therapy and its relationship to the patient's posttreatment quality of life.

Successful reconstruction requires accurate preoperative assessment and formulation of an individualized treatment plan. Careful consideration of a variety of factors is essential, the most important of these factors is the nature of the defect of the head and neck. Other important considerations include the following: (1) specific histologic features of the tumor, clinical stage, and associated prognosis; (2) age, sex, body habitus, and associated health problems of the patient; (3) available flap donor sites; (4) available recipient vessels; (5) patient compliance with perioperative care, patient expectations, and the psychosocial needs of the patient; and (6) clinical experience and skills of the surgeon. Consequently, a rigid "cookbook," algorithm-based approach for reconstruction of the head and neck is ill advised. Superior results are seen when the reconstructive team has a wide range of options, which permits the reconstruction to be customized to the individual patient, based on careful consideration of all pertinent tumor- and patient-related factors. Hence, just as the overarching approach to contemporary cancer management has stressed individualized treatment strategies, so too has the approach to reconstruction. In addition, it has been our experience that a multidisciplinary approach to the patient's reconstructive surgery and rehabilitation provides an opportunity for optimal outcomes. This approach begins in the preoperative planning stage and parallels the multidisciplinary approach to the overall cancer management.

GOALS OF RECONSTRUCTION

The primary goal of treatment of cancer of the head and neck is to effect a cure or significant palliation. In addition, every effort should be made to restore the patient to the premorbid level of functioning and quality of life. Advances in radiation and chemotherapy have altered the approach to cancers arising in many subsites of the upper aerodigestive tract, where surgery has been relegated to the salvage setting to eradicate persistent or recurrent

cancers. When surgery is used, especially in the oral cavity, it often involves surgical ablation of the primary site and removal of regional nodal metastases. Except in rare cases, some form of reconstruction is necessary. No reconstructive procedure, however elaborately or creatively conceived, should preempt adequate tumor resection nor should such a plan be rigidly adhered to if events during the ablation dictate that an alternative approach will result in a preferred oncologic outcome.

For the reasons outlined above, contemporary reconstruction of the head and neck often takes place in patients who have undergone prior radiation therapy. This is particularly true in the management of complications of radiation therapy such as osteoradionecrosis (ORN) and pharyngoesophageal stenosis.[6–8] The reconstructive surgeon must adopt a unique approach in patients with prior radiation therapy to the head and neck region, as there are significant wound healing challenges that can pose a threat to the safety of the surgical undertaking as well as impacting the ultimate functional and aesthetic outcomes.

Successful reconstruction of defects in the head and neck requires that the surgeon define the nature of the defect and create an appropriate strategy to replace the resected tissues with an appropriate substitute.[9] Each subsite of the head and neck presents unique challenges and requires different reconstructive approaches. The major subsites include the cranial base, radical parotidectomy, palatomaxillary, oromandibular, oropharyngeal, and laryngopharyngeal defects. Cutaneous defects of the head and neck may result from management of skin cancer or direct extension to the skin from cancers arising in underlying tissues. Optimal results usually require reconstruction with tissues that simulate the appearance and function of the resected tissue. The tissues required to achieve these goals may include the following: (1) epithelium, to resurface a mucosal or skin defect; (2) muscle, to restore motion or provide coverage of irradiated tissues; and (3) bone, to provide skeletal support. Less frequently, tissues such as fascia and adipose tissue may be required for static suspension or for restoration of contour. Complex defects of the head and neck, such as those resulting from oromandibular and cranial base resection, may require reconstruction with a composite flap. It is in such cases that microvascular free tissue transfer has been most widely used.

The first priority in reconstruction of defects in the head and neck should

be safety. It is essential to prevent life-threatening complications, such as carotid blowout, or cerebrospinal fluid (CSF) leak and subsequent meningitis, after resection of the cranial base. The next priority is to return the upper aerodigestive tract to a functional state. Restoration of oral competence, mastication, deglutition, and articulation are the major objectives of reconstruction of the oral cavity following ablative surgery. Maintaining mobility of the tongue, restoring occlusal relationships, preventing trismus, and setting the stage for functional dental rehabilitation are the specific strategies to achieve those goals. Advances in dental prosthetics and the ability of surgeons to reliably transfer vascularized bone have been essential in this regard.

Surgeons should be sensitive to the impact of physical appearance on the patient’s sense of well-being and to the patient’s ability to reintegrate into the society of their family, friends, and work environment. Reconstruction with local tissue is preferred for cutaneous defects because skin adjacent to the defect provides the optimal match in color and texture. If local tissue is unavailable, the skin quality of potential flaps to be transferred from regional or distant donor sites should be considered. Similarly, when maintenance of bulk in the flap is important aesthetically, the progressive atrophy of denervated muscle should be anticipated. The use of well-vascularized subcutaneous adipose tissue may provide a more effective long-term result. Aesthetic units should be managed as a total entity when possible, especially in resurfacing of defects of the cheek, nose, lips, forehead, and less critically, the neck. To maximize the aesthetic result in the patient with cancer of the head and neck, adjunctive procedures, such as scar revision and flap recontouring, can be performed subsequent to the initial reconstructive effort.

The patient’s age, comorbid conditions, disease status, and motivation may relegate the aesthetic outcome to a secondary concern, whereas functional outcomes are almost always of paramount importance. Defects of the oral cavity and oropharynx, especially those involving the tongue and palate, frequently require more elaborate techniques for the restoration of effective articulation and deglutition. Maintenance of a patent pharyngoesophageal segment and restoration of velopharyngeal competence are vital to achieving optimal functional outcomes. Understanding the function of the ablated tissues and the underlying physiology of the region helps to guide the surgeon in selecting the appropriate strategy for each

patient.

PREOPERATIVE PLANNING AND TIMING OF RECONSTRUCTION

Comprehensive management of patients with cancer of the head and neck begins with thorough preoperative planning. For select defects, multidisciplinary planning and implementation of the treatment approach can help to ensure that the best possible outcome is achieved. Patients with cancer typically present with numerous comorbidities and risk factors, including cardiac, renal, pulmonary, cerebrovascular, and hepatic disease. Malnutrition and general debility, secondary to the disease process or to previous surgery, radiation, or chemotherapy, are also common. A thorough initial history, review of systems, and physical examination should provide an evaluation of these risk factors that can be augmented with additional diagnostic studies. An assessment of cardiopulmonary risk factors, especially coronary artery disease, is essential in determining whether a patient is a candidate for a more elaborate reconstructive approach that includes microvascular surgery. Postoperative cardiopulmonary instability can be a threat to the patient and to the reconstructive effort. Mapping of the extent of the primary cancer by a combination of physical examination and radiographic assessment allows the reconstructive surgeon to estimate the probable extent of resection and consideration of the most likely reconstructive approach. In select cases, examination under anesthesia can provide extremely valuable information as to the expected extent of the resection.

The anticipated defect should be classified according to its osseous, soft tissue, and neurologic components. Consideration of the functional region encompassed by the deficit is of far greater importance than a description of the total area or volume of tissue involved. The possible need for coverage of the carotid artery or dura is also discussed. If free tissue transfer is contemplated, potential donor sites and recipient vessels should be evaluated to assess their suitability. Based on all available information, a reconstructive plan is formulated. A second, and even a third, “fallback” option should be considered in the event that the initial plan proves to be unfeasible or fails during the postoperative period.

Reconstruction of the maxilla and mandible may be optimized through

the use of computer-generated medical models. In select clinical situations, the creation of a medical model can greatly enhance the efficiency and the accuracy of the surgical plan. The most common instances where we have found medical models to be useful are for patients with existing segmental defects of the mandible and maxilla and for patients with tumors that significantly distort the normal bone contour, making fabrication of a rigid fixation plate difficult. The ability of computerized planning to accurately create a surgical model represents a major advance and one that should be anticipated in the preoperative period. The importance of this approach is due to the fact that the computer planning software can reestablish the normal "predisease" shape of the jaw that allows for a more precise plate contouring and a more accurate replication of the patient's normal facial contour (**Fig. 28.1**).

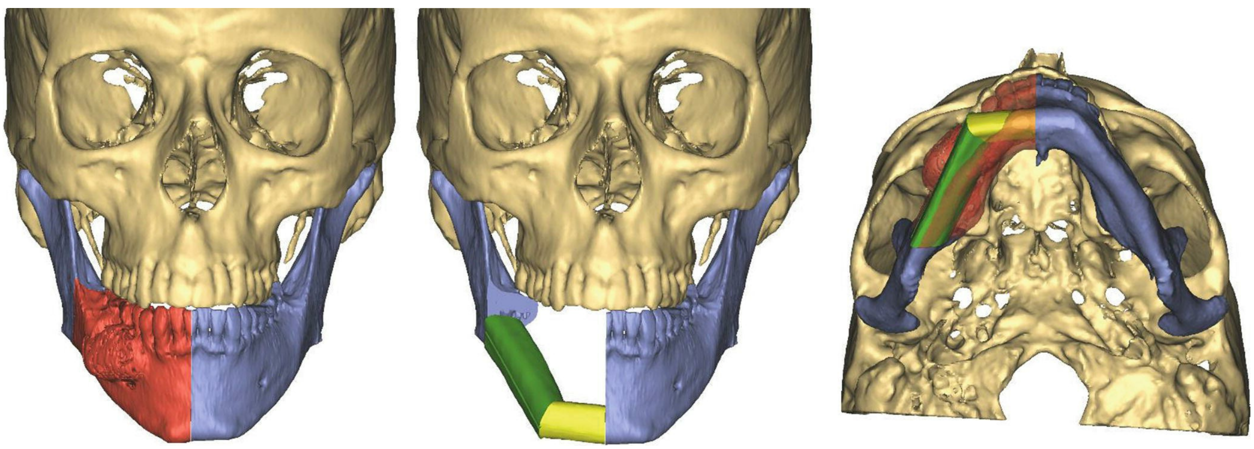


Figure 28.1. Computer-generated plan for reconstruction of a segmental right mandible defect with buccal cortex distortion.

Most reconstructive procedures in the head and neck are optimally performed in one stage at the time of ablation. Primary reconstruction, although lengthening the surgical procedure, provides an opportunity to introduce the necessary elements of the reconstruction and to ensure the highest likelihood of a safe and successful postoperative recovery. Optimal conditions for reconstruction are present at the completion of tumor resection: (1) the defect is widely exposed; (2) bone and soft tissue requirements are readily and accurately assessed; and (3) potential recipient vessels for microvascular anastomoses, if indicated, are already dissected. Furthermore, surgical margins can be cleared by frozen section pathologic analysis, which

permits definitive wound repair. This approach avoids the problems associated with delayed reconstruction, including fibrosis of remaining muscles and contraction of soft tissues within the wound bed. Consequently, primary reconstruction has been shown to provide superior functional and aesthetic results when compared with delayed reconstruction. In addition, the attitude of patients undergoing primary reconstruction is greatly improved when maximal form and function are promptly restored.

Certain reconstructive procedures of the head and neck, however, should be performed in a staged or delayed manner. Multistaged repairs of complex nasal and auricular defects are prime examples. In these instances, the surgeon should plan to perform the fewest number of procedures necessary to obtain optimal results in the shortest possible time. In cases in which tumor-free margins are in question, reconstruction should be delayed until permanent pathologic confirmation is made. Frequently, the functional and cosmetic results of an elaborate reconstructive effort can be maximized by subsequent revisions. These secondary procedures may include scar revision, flap debulking, and placement of endosteal dental implants for dental rehabilitation.

RECONSTRUCTIVE OPTIONS

In general, the least complex method that provides a safe reconstruction while restoring form and function should be selected. The reconstructive surgeon should first consider primary closure or the use of a skin graft. Larger defects usually require alternative methods, such as local, regional, or distant (free) flaps. This logical progression from simple to more complex techniques provides a systematic approach for evaluating whether a given technique satisfies the functional and cosmetic requirements of each defect in the head and neck.

Local Flaps

Local flaps are effective reconstructive alternatives for certain small- to medium-sized defects of the face, neck, and upper aerodigestive tract. When used judiciously, local tissue transfer is aesthetically and functionally superior to the use of more elaborate regional or distant free flaps. The use of tissue adjacent to the defect often provides the best match of skin in terms of

its color and texture.

The size and location of the defect and the properties of the available local tissue help to determine whether a local flap is an appropriate reconstructive method. The vascular supply of each local flap is unique and dictates the amount of tissue that can be reliably transferred. Defects of the nose and lips are optimally reconstructed with local muscle-skin flaps, such as forehead, nasolabial, Abbé-Estlander, and Karapandzic flaps. Small intraoral defects can be closed with palatal and buccal mucosal flaps.[10] A more detailed description of the various local flaps is beyond the scope of this chapter.

Regional Flaps

Large defects in the head and neck can be reconstructed with tissues from adjacent regions. Pedicled regional flaps have been used extensively to provide closure of large defects in the neck, face, scalp, oral cavity, and pharynx. They can be classified as fasciocutaneous, such as the deltopectoral flap and the submental island flap, or myocutaneous, such as the pectoralis major, trapezius, and latissimus dorsi flaps. In additional, the temporoparietal fascial flap can be raised as purely a fascial flap or in conjunction with the overlying skin. The temporalis muscle flap is a valuable source of vascularized muscle in the reconstruction of the infratemporal fossa, skull base, and orbitozygomatic defects. Most regional flap procedures can be performed in one stage. However, a “delay” may be instituted to more reliably increase the overall size of the flap. For most cutaneous defects of the neck, the thin, supple quality of the deltopectoral flap is preferred. However, for coverage of the carotid artery or reconstruction of a large oropharyngeal defect, the additional bulk and reliable vascular supply of a myocutaneous flap are advantageous. The arc of rotation is another intrinsic property that must be considered. Only the pedicled latissimus dorsi and lower island trapezius flaps have an extensive arc of rotation that can reliably reach large defects of the scalp. The selection of a specific regional flap depends on the location and size of the defect and the intrinsic properties of the regional flap.

Deltopectoral Flap

The deltopectoral flap is a medially based axial-pattern fasciocutaneous flap of the upper chest that is based on the second and third intercostal,

parasternal, perforating branches of the internal mammary artery. The distolateral extent of the flap is determined by the location of the defect relative to the rotational length of the flap; however, distal flap necrosis occurs frequently when the flap is extended onto the shoulder beyond the deltopectoral groove. If greater flap length is desirable, a delay procedure is often necessary to incorporate a random portion of skin over the deltoid muscle.[11]

The deltopectoral flap is primarily used for resurfacing cutaneous defects of the neck. The introduction of other regional or distant tissue transfer has limited the role of the deltopectoral flap for facial, oral, and pharyngeal reconstruction. Nonetheless, it remains a useful tool for selected reconstructive needs. Although traditionally harvested as a peninsula of skin, it can also be modified as an "island configuration" and tunneled into the neck beneath the skin of the upper chest. This produces a more pleasing contour to the neck and a more favorable reconstructive outcome.

The Submental Island Flap

The submental island flap provides tissue that satisfies the color and texture requirements of the facial skin. It is a reliable and useful flap in reconstruction of the cutaneous defects in the lower and middle thirds of the face. A flap up to 6 to 8 cm in vertical height can be harvested and primary closure achieved, especially in older individuals with older patients with increased skin laxity (**Fig. 28.2**). The flap is based on the submental branch of the facial artery, which must be carefully preserved. Potential for injury to this vessel during level IB dissection may limit the use of the flap when supraomohyoid neck dissection is indicated for oncologic reasons. Proximal ligation of the facial artery and vein with retrograde flow designed can enhance the arc of rotation of the flap.

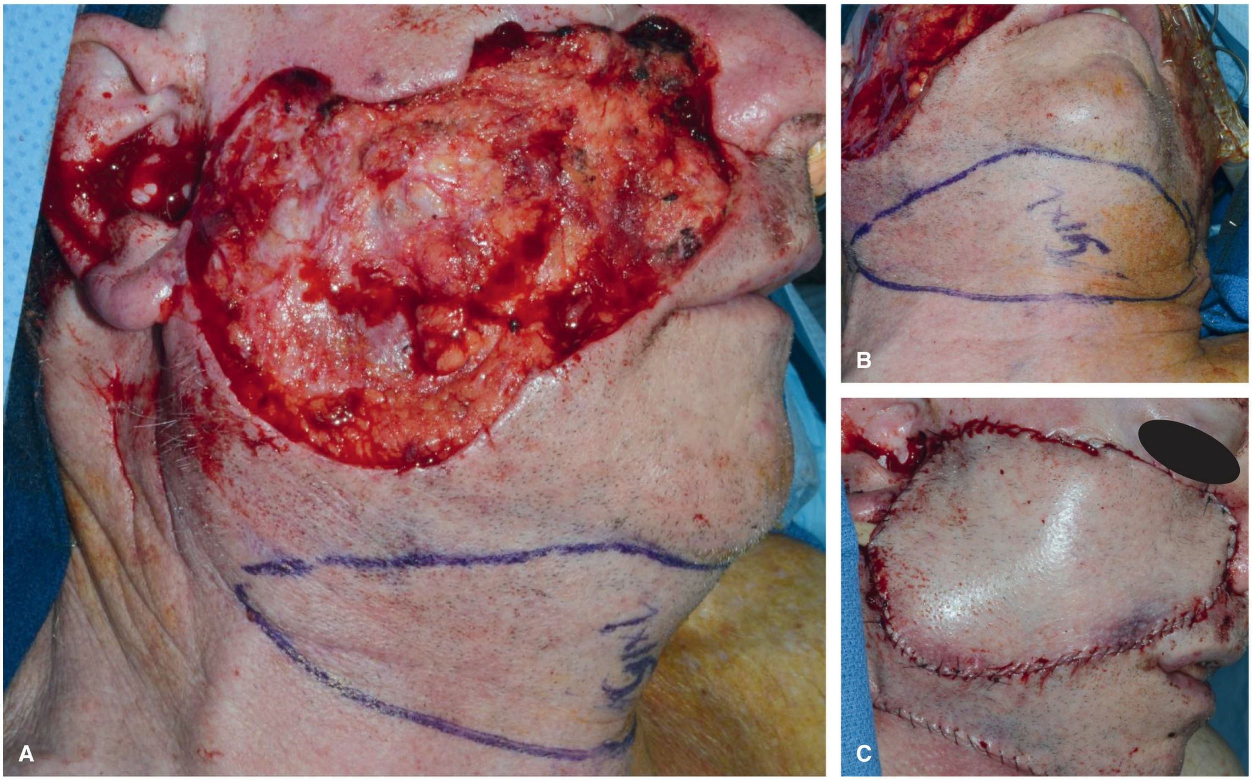


Figure 28.2. A and B: Submental flap is marked for the reconstruction of a large lower face defect. The horizontal dimension extends from angle to angle of the mandible. Vertical dimension is limited by the “pinch test.” **C:** Tension-free closure is achieved.

Myocutaneous Flaps

These axially based flaps have segmental vascular pedicles that enter the deep surface of the muscle, course longitudinally, and send perforating branches through the muscle and subcutaneous tissue to the overlying skin. A large amount of well-vascularized tissue can be transferred in a single stage to reconstruct almost any defect in the head and neck, from the pharyngoesophagus to the lateral skull base.

Despite their widespread use, regional myocutaneous flaps have certain disadvantages. In defects that require thin, pliable skin, the excess bulk of a myocutaneous flap may lead to a less than optimal result. Regional myocutaneous flaps have limited length, skin paddle size, and arc of rotation. The sacrifice of a regional muscle to provide a vascular supply to the overlying skin may result in some degree of functional disability as well as in moderate distortion of the anterior chest or back.

Pectoralis Major Flap.

The pectoralis major originates from the medial one-third of the clavicle (cephalic portion), the sternum and cartilages of the upper six ribs (central or sternocostal portion), and the external oblique aponeurosis (caudal portion). The primary vascular supply is from the pectoral branch of the thoracoacromial artery, with a lesser contribution from the lateral thoracic artery.

The pectoral branch of the thoracoacromial artery is visualized on the undersurface of the pectoralis major muscle and enters the muscle medial to the tendon of the pectoralis minor, whereas the lateral thoracic artery courses lateral to the tendon. In most instances, the pectoralis major muscle and the overlying skin are passed over the clavicle into the neck. In rare circumstances, a tunnel deep to the clavicle, created by removing and repositioning a small portion of the clavicular bone may be warranted.[12]

When first introduced, the pectoralis major flap was used primarily for reconstruction of mucosal defects of the oral cavity and pharynx and cutaneous defects of the neck. As previously mentioned, the pectoralis major flap is still considered the "workhorse" for head and neck reconstruction especially in settings where resources are limited and/or microvascular reconstruction is not available. In places where microvascular reconstruction is available, the pectoralis major flap plays an important role, especially in the setting of salvage surgery. It can be used to provide muscle coverage over the carotid artery or to supplement microvascular reconstruction. The pectoralis major muscle can also obliterate dead space, for example, after mediastinal dissection. The pectoralis major myocutaneous flap is extremely reliable, as indicated by a low incidence of reported complications. The incidence of total flap necrosis has been reported as 1% to 3%.[13] The incidence of partial flap necrosis, as high as 30% in some series, is probably related to the degree of caudal extension of the skin paddle over the rectus sheath. Depending on the patient's body habitus, the pectoralis flap may be less reliable for more cephalic defects of the face, scalp, and pharynx. Furthermore, the effect of gravity on the bulky pectoralis major muscle may be detrimental, especially when the flap is placed in an unfavorable recipient bed or when a patient is at risk for compromised wound healing.

Trapezius Flaps.

The trapezius muscle is a broad, thin, triangular muscle that covers most of the upper back and posterior neck. The vascular supply of the trapezius muscle is more complex and variable than that of the other regional myocutaneous flaps used for reconstruction in the head and neck. The dominant blood supply is from the transverse cervical artery (TCA), which consists of a superficial branch and a deep branch. The deep branch of the TCA is also known as the dorsal scapular artery (DSA). Lesser contributions from the occipital artery and the posterior intercostal perforators are also present.

Of the three distinct trapezius flaps, the superior trapezius flap[14] is the most reliable. The primary blood supply is from the paraspinous perforators with some contribution from the occipital artery and the ascending branch of the superficial branch of the TCA. Unlike the other trapezius flaps, its blood supply is unaffected by prior radical neck dissection with sacrifice of the transverse cervical vessels. The superior trapezius flap is used primarily for protection of the carotid artery and for the resurfacing of lateral cervical cutaneous defects (**Fig. 28.3**). Because it is superiorly based, the effect of gravity does not cause the flap to pull away from the bed. The donor site usually cannot be closed primarily, and therefore, a skin graft is needed. Also, a dog-ear correction is often required.

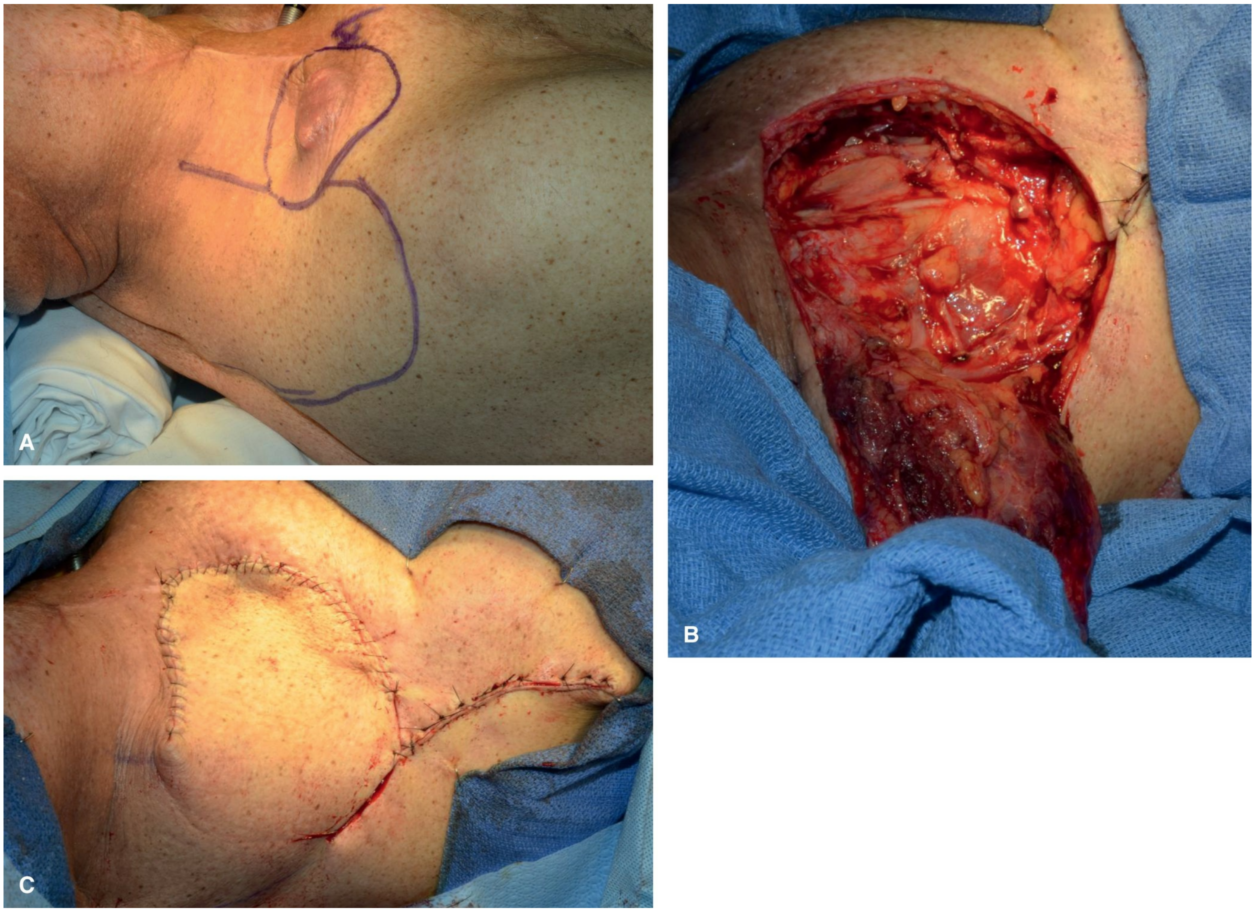


Figure 28.3. A: Superior trapezius rotational flap planned for the reconstruction of a cutaneous defect overlying the supraclavicular fossa. **B**: The flap is pedicled superomedially on the paraspinous perforators. **C:** Tension-free closure is achieved.

The lateral island trapezius flap[15] is based on the TCA. It can reach the anterior neck, oral cavity, and pharynx in some cases, but its arc of rotation is dependent on favorable vascular anatomy of the transverse cervical system in the posterior triangle of the neck and the degree of mobilization of the TCA and TCV. Because of this variable vascular anatomy, preliminary exploration of the posterior triangle is essential. If the TCA is coursing deep to the brachial plexus, it will be impossible to mobilize the lateral island trapezius flap. Following harvest of this flap, wide undermining should allow primary closure of the donor site defect.

The lower island flap[16] is the most versatile with the greatest arc of rotation of the three trapezius myocutaneous flaps. The skin paddle is designed over the inferior third of the trapezius muscle, between the vertebrae

and the scapula. The superior arc of rotation of this flap permits reliable closure of defects in the posterior neck, temporal bone, and scalp (**Fig. 28.4**). Less frequently, it has been used for reconstruction in the oral cavity and pharynx. The major disadvantage of the lower island flap is the necessity of placing the patient in the lateral decubitus position for the flap harvest.

Figure 28.4. A: Lower island trapezius flap is used in the reconstruction of a postauricular cutaneous defect. **B:** Tension-free closure is achieved as a result

of a large arc of rotation. **C:** Skin color match is adequate.

Latissimus Dorsi Flap.

When all pedicled myocutaneous flaps are considered, the latissimus dorsi flap has the largest potential skin area (25 × 40 cm) available for transfer to the head and neck.[17]–[20] Two separate cutaneous paddles may be designed based on the intramuscular bifurcation of the thoracodorsal vascular pedicle for reconstruction of through-and-through defects. The functional disability that results from the transfer of the latissimus dorsi muscle is reportedly less than that resulting from the use of either the pectoralis or the trapezius muscle.[18] This flap is frequently transferred as a free flap, and details relevant to the anatomy, surgical technique, and clinical application of the latissimus dorsi flap are discussed further in the following section on the Scapular System of Flaps.

Temporoparietal Fascia Flap

The thin and pliable tissue of the temporoparietal fascial flap is useful for lining of defects in the upper face where excess bulk is undesirable. Its location makes it invaluable in the reconstruction of auricular defects, and its thinness and pliability allow the cartilaginous architecture to be revealed. Variations in flap harvest include incorporation of the forehead or scalp skin and, less frequently, vascularized split calvarium bone. The integrity of the superficial temporal vascular pedicle is essential to ensuring flap viability.

Temporalis Muscle Flap

The temporalis muscle receives its main vascular supply from the anterior and deep temporal artery branches of the internal maxillary artery. It is used in reconstruction of the skull base, the infratemporal fossa, and the maxillectomy defects. Although employed extensively in the past, the use of this muscle in facial reanimation is currently limited to temporalis tendon transfer for suspension of the lower lip. The primary disadvantages of this donor site include a fairly limited reach and the resultant hollowing in the temporal area.

Microvascular Free Tissue Transfer

One of the most important benefits of free tissue transfer is the superior blood supply that maximizes tissue survival and wound healing in unfavorable, contaminated head and neck recipient sites. Thus, it promotes healing despite scarring, radiation damage, and salivary contamination of the recipient bed. The second major benefit relates to the freedom of being able to inset a free flap without being restricted by a limited vascular pedicle, as is common with regional flaps. The skin islands of the pedicled pectoralis major, trapezius, and latissimus flaps are often transferred from the distal and least vascular portions of the territory. Free tissue transfers are more efficient in that the flap can be placed into the defect with less concern for distal flap necrosis. Also, certain recipient sites, in particular the scalp and cranial base, may be beyond the reliable reach of most regional flaps. Even if a regional myocutaneous flap reaches the defect, the effect of gravity on the pedicle may place additional tension on a tenuous suture line.

Another advantage of free flaps is the greater variety and versatility of donor sites. Free tissue transfers such as the scapula megaflap or the iliac crest-internal oblique flap permit the harvesting of multiple tissue paddles based on a single vascular pedicle. Thus, free tissue transfers can be designed to restore more complex defects more precisely than can the tissues from adjacent regional donor sites. The disadvantages of free tissue transfer arise from the complexity of the technique and the increased surgical time required. As with regional pedicled flaps, the color and contour of free flaps in certain cases may not exactly match those of the recipient site. If the patient is a poor surgical risk, a more expedient and less complex technique that uses a regional flap may offer a safer reconstructive alternative.

It is essential that the characteristics of various free tissue transfer approaches be carefully considered[21] (**Tables 28.1** and **28.2**). Several anatomic areas, including the groin, abdomen, back, and extremities, provide reliable fasciocutaneous, musculocutaneous, and osteomusculocutaneous flaps. Each donor site has inherent advantages and disadvantages. For vascularized, bone-containing free flaps, the amount of bone stock available and the flexibility of the soft tissue component in relation to the bone are important considerations. The morbidity incurred at the donor site following free flap harvest must also be taken into account.

Table 28.1 Free Tissue Transfer Donor Sites: Anatomic Details

	Blood Supply	Pedicle Length	Artery Diameter	Vein Diameter	Nerve Supply
Fasciocutaneous Free Flap					
Radial forearm	Radial artery	18 cm (range of 15–22 mL)	3 mm (range 2.5–3.5 mm)	1.5 mm (range 1–2 mm)	Medial and lateral antebrachial cutaneous nerves
Lateral arm	Radial collateral artery of the profunda brachii artery	6 cm (range 4–8 cm)	1.5 mm (range 1–3 mm)	2.5 mm (range 1.5–3 mm)	Lateral brachial cutaneous nerve
Anterolateral thigh	Lateral circumflex femoral artery	12 cm (range 8–16 cm)	2.1 mm (2–2.5 mm)	2.3 mm (range 1.8–3.3 mm)	Lateral femoral cutaneous nerve
Scapula/ parascapula	Axillary artery → subscapular artery → circumflex scapular artery	10–12 cm	4 mm	Large diameter	3rd–5th intercostal
Myocutaneous Free Flap					
Rectus abdominis	Deep superior epigastric artery (DSEA), deep inferior epigastric artery (DIEA)	Deep inferior epigastric artery (DIEA) 7 cm (range 6–8 cm)	Deep inferior epigastric artery (DIEA) 3.5 mm (range 3–5 mm)	Deep inferior epigastric vein (DIEV) 4 mm (range 2–5 mm)	7th–12th intercostals
Gracilis	Branch of the medial femoral circumflex artery or profunda femoral artery	7 cm (range 6–8 cm)	1.5 mm (range 0.5–2 mm)	1.5–2.5 mm	Motor: anterior branch of obturator nerve Sensory: medial cutaneous nerve of the thigh
Latissimus dorsi	Axillary artery → subscapular artery → thoracodorsal artery	8.5 cm (range 6.5–12 cm)	3 mm (range 2–4 mm)	3.5 mm (range 2–5 mm)	Motor: thoracodorsal nerve Sensory: intercostals
Vascularized Bone-Containing Free Flap					
Fibula	Peroneal artery	2 cm (range 2–4 cm)	1.5 mm (range 1–2.5 mm)	3 mm (2–4 mm)	Lateral sural nerve
Iliac crest	Deep circumflex iliac artery	9 cm (range 8–10 cm)	2.8 mm (range 2–3 mm)	3.6 mm (range 2–5 mm)	T12 nerve
Scapula	Axillary artery → subscapular artery → circumflex scapular artery	10–12 cm	4 mm	Large diameter	3rd–5th intercostal
Radius	Radial artery	18 cm (range of 15–22 mL)	3 mm (range 2.5–3.5 mm)	1.5 mm (range 1–2 mm)	Medial and lateral antebrachial cutaneous nerves
Visceral Free Flaps					
Jejunal	Jejunal artery	5 cm (range 4–6 cm)	2 mm (range 1.5–2.5 mm)		
Gastro-omental	Right and left gastroepiploic artery	30 cm	Right artery 1.5–3 mm; left artery 1.2–2.9 mm		

Table 28.2 Free Tissue Transfer Donor Sites: Advantages and Disadvantages

	Advantages	Disadvantages	Ease of Dissection	Donor Site Morbidity
Fasciocutaneous Free Flap				
Radial forearm	Constant, reproducible vascular anatomy, two-team approach; long pedicle with large-diameter vessels	Requires skin graft unless cutaneous flap <2–3 cm	Easy	Maximal
Lateral arm	No risk to vascular anatomy of the hand; two-team approach	Donor site complications (pain, hyperesthesia)	Easy	Minimal
Anterolateral thigh	Long length and large pedicle; two-team approach	Color mismatch for facial reconstruction	Easy	Moderate
Scapula/parascapula	Color of the back may provide a better match than the radial forearm or thigh: extremely reliable.	Harvest requires lateral decubitus positioning.	Moderate	Minimal
Myocutaneous Free Flap				
Rectus abdominis	Skin island versatile (can be transverse, vertical, and/or oblique); two-team approach	Risk of herniation	Easy	Can be significant
Gracilis	Easy dissection; facial reanimation flap; two-team approach; scar well concealed	Skin island not reliable	Easy	None
Latissimus dorsi	Largest single flap that can be harvested	Flap can be bulky, lateral decubitus position.	Easy	Minimal
Vascularized Bone-Containing Free Flap				
Fibula	20–26 cm of bone may be harvested in adults: two-team approach.	Donor scar obvious; ankle dysfunction with aggressive physical activity	Easy	Limited
Iliac crest	10–16 cm of bone length available; skin paddle as large as 16 x 20cm; bone ideal for mandibular reconstruction; two-team approach	Risk of herniation/hematoma; dissection can be lengthy, tedious; skin paddle often thick and bulky, gait disturbance	Difficult	Sometimes significant
Scapula	Color of the back may provide a better match than radial forearm or thigh: extremely reliable.	Harvest requires lateral decubitus positioning.	Moderate	Minimal
Radius	Tremendous soft tissue versatility with long vascular pedicle and 10–12 cm of vascularized bone for intraoral defects	Major risk is fracture of remnant radius (can minimize risk by limiting harvest to 40% of circumference and plating remnant bone).	Easy	Maximal
Visceral Free Flaps				
Jejunal	Jejunum diameter approximates esophagus; as a free flap, the vascular pedicle can be lengthy (15–20 cm): two-team approach.	Require laparotomy	Easy	Laparotomy needed
Gastro-omental	Gastric mucosa is readily fashioned to repair pharyngeal defects; omentum can be used to provide carotid artery coverage and augment soft tissue.	Require laparotomy	Moderate	Laparotomy needed

Fasciocutaneous Free Flaps

Fasciocutaneous free flaps provide a segment of skin and subcutaneous adipose tissue of variable size and thickness for reconstruction of a wide variety of frequently encountered defects. Flaps commonly used for head and neck reconstruction include (1) the radial forearm flap, (2) the lateral arm flap, (3) the anterolateral thigh flap, and (4) the scapular and parascapular flaps (see under Scapular System of Flaps). The pliability of these flaps

allows for precise anatomic restoration of resected tissue during oral cavity, oropharyngeal, and hypopharyngeal reconstruction. The radial forearm, lateral arm, and anterolateral thigh flaps have the potential for sensory reinnervation, which may be helpful for the rehabilitation of mastication and deglutition in oral cancer patients. Because adipose tissue within revascularized flaps does not atrophy, fasciocutaneous flaps allow for precise and permanent restoration of contour deformities.

Radial Forearm Flap.

The radial forearm free flap is a fasciocutaneous flap that is harvested from the volar aspect of the forearm. It provides a large amount of thin, pliable skin that has the potential for sensory reinnervation via the antebrachial cutaneous nerves. Consequently, it has become the free tissue transfer of choice for the resurfacing of oral cavity and oropharyngeal defects.[22] It has also gained considerable popularity for reconstruction of the hypopharynx and cervical esophagus. In select situations, it has also been used to resurface the scalp and a variety of areas of the face, including the cheek, nose, chin, and forehead.

The radial forearm flap has numerous advantages:

1. It provides a large amount of relatively thin, often hairless, skin that can be folded on itself to conform to nearly any mucosal or cutaneous defect.
2. It has a long vascular pedicle and vessels of large size, facilitating dissection and revascularization.
3. Sensation can be restored to the skin paddle by the incorporation of the medial or lateral antebrachial cutaneous nerves.[23,24]
4. The donor site permits simultaneous two-team harvest and dissection under tourniquet control.
5. A moderate amount of subcutaneous adipose tissue can be left attached to the vascular pedicle, either for protection of the great vessels and the flap’s vascular pedicle or for augmentation of contour deformities, such as those seen following radical neck dissection.
6. The radial forearm flap can also be used as an osteocutaneous free flap because a 10- to 12-cm-long bone segment encompassing 40% of the circumference of the radius can be harvested with the skin paddle.[25]

However, when used as an osteocutaneous flap for mandibular or maxillary reconstruction, the limited bone stock restricts the potential for

functional dental restoration.

The disadvantages of the radial forearm free flap are primarily aesthetic. Unless extremely small, the forearm donor defect requires skin grafting. In addition, the color and texture match to facial skin is only fair. A potentially devastating complication of the radial forearm flap is vascular compromise of the hand. To avoid this complication, a preoperative Allen's test is essential to assess the circulation of the hand. Other complications include insufficient flow to the hand despite a normal Allen's test, numbness of the hand as a result of trauma to the superficial branches of the radial nerve, devastating infection resulting in suppurative tenosynovitis, and poor take of the skin graft secondary to failure to preserve the paratenon over the flexor tendons, leading to exposure of the forearm tendons as a result of incomplete healing of the skin graft over the donor defect.

Lateral Arm Flap.

Although this flap is harvested most frequently as a fasciocutaneous flap,[26] it can also be raised with a monocortical segment of vascularized humerus, triceps tendon, or brachialis muscle. Alternatively, the flap can be de-epithelialized and used as a vascularized fascia-adipose tissue flap for soft tissue augmentation. Dye injection studies indicate that the lateral arm flap can incorporate a cutaneous paddle that ranges from 8 × 10 cm to 14 × 15 cm. The width of skin that is harvested with the lateral arm flap is usually limited to 6 to 8 cm or one-third of the circumference of the arm, which is the largest cutaneous defect that can be closed primarily.

In the head and neck region, the lateral arm flap has been used most frequently for facial and intraoral reconstruction.[27,28] For soft tissue augmentation, it is of intermediate thickness relative to the thin radial forearm flap and the thicker anterolateral thigh and scapular system of flaps.

The lateral arm flap has several advantages over other fasciocutaneous flaps commonly employed in head and neck reconstruction. Unlike the radial forearm flap, which requires harvesting of the radial artery, harvesting of the posterior radial collateral artery (PRCA) with the lateral arm flap poses no risk for limb ischemia, and the donor site rarely requires a skin graft. Unlike the scapular fasciocutaneous flap, the lateral arm flap may be harvested with the patient in the supine position, allowing a simultaneous two-team approach.

Relative disadvantages of the lateral arm flap include a linear scar on the lateral aspect of the arm and anesthesia of the forearm as a result of transection of the posterior cutaneous nerve to the forearm. Dissection of the vascular pedicle of the lateral arm flap can be more tedious than harvesting procedures for the radial forearm or scapular fasciocutaneous flaps. This pedicle has an average length of 4 to 8 cm, which limits its application to certain head and neck defects.

Anterolateral Thigh Flap.

The anterolateral thigh flap is a fasciocutaneous flap that is harvested from the anterior thigh in the area overlying the septum between the rectus femoris and the vastus lateralis muscles. It is based on the descending branch of the lateral circumflex femoral artery and its venae comitantes. The vascular pedicle can be up to 16 cm in length with large-diameter vessels. Primary closure of the donor site can usually be achieved, even following the harvest of large skin paddles. Sensory reinnervation is possible with incorporation of the lateral cutaneous nerve of the thigh. Due to these features, it has become quite popular for use in reconstruction in the head and neck.[29,30]

The anterolateral thigh flap is often used in pharyngoesophageal defects or other large mucosal defects. Its advantages include a large area of skin for harvest and a relatively straightforward dissection with minimal donor site morbidity. Its location allows for an easy two-team approach, and no special positioning is required.

Disadvantages of this flap include excessive flap thickness in obese patients, the potential for hair-bearing skin in men, and the necessity to take a cuff of vastus lateralis muscle in 60% of patients in whom the skin is supplied by perforators that traverse the muscle rather than by a pure septocutaneous route.[31]

Myocutaneous Free Flaps

Myocutaneous free flaps are a versatile reconstructive tool for the head and neck surgeon because they provide bulky tissue with reliable vascularity to the overlying skin and offer distinct advantages over regional myocutaneous flaps, namely, a greater versatility in design and the 3-dimensional freedom of maneuverability for flap insetting. Their use is most appropriate for the reconstruction of extensive defects of the tongue, scalp, skull base, and

paranasal sinuses. In addition, some free muscle flaps can be reinnervated for reanimation of the paralyzed face. The most commonly used musculocutaneous free flaps include (1) rectus abdominis, (2) gracilis, and (3) latissimus dorsi (see under Scapula System of Flaps).

Rectus Abdominis Flap.

A unique feature of the rectus abdominis flap is that a substantial amount of muscle and skin can be harvested. Musculocutaneous perforators are located in the periumbilical region and oriented toward the inferior border of the scapula. Because of these perforators, the skin of a significant portion of the abdomen may be transferred reliably.[32]

The rectus abdominis flap is one of the most versatile and commonly performed free tissue transfers in head and neck reconstruction.[33] It is used frequently when bulky soft tissue is required for reconstruction. For example, it is useful following total glossectomy. One of its greatest uses is in skull base reconstruction, especially in an irradiated patient, to prevent a CSF leak and an ascending infection and to provide vascularity to a free calvarial bone graft.

The rectus abdominis flap offers numerous advantages:

1. Its primary vascular pedicle—the deep inferior epigastric artery and vein (DIEA, DIEV)—is long and of large diameter.
2. It can be harvested with the patient in the supine position, allowing a two-team approach.
3. A large amount of tissue can be harvested and primary closure of the donor defect can still be achieved (**Fig. 28.5**).
4. The rich vascularity of the abdominal wall allows great flexibility in the design of the paddles. Multiple skin paddles of varying thickness, based on the periumbilical perforating vessels, can be designed for use in the reconstruction of complex three-dimensional defects. The skin paddles can be oriented in a transverse, a vertical, or an oblique direction.
5. Donor site morbidity is minimal, as long as the rectus fascia is repaired to prevent formation of a ventral hernia.
6. The durable anterior rectus fascial sheath and tendinous inscriptions facilitate placement of sutures during insetting of the flap. This allows for a watertight closure and obliteration of dead space, which are critical in the oral cavity and in reconstruction of the cranial base.[34]

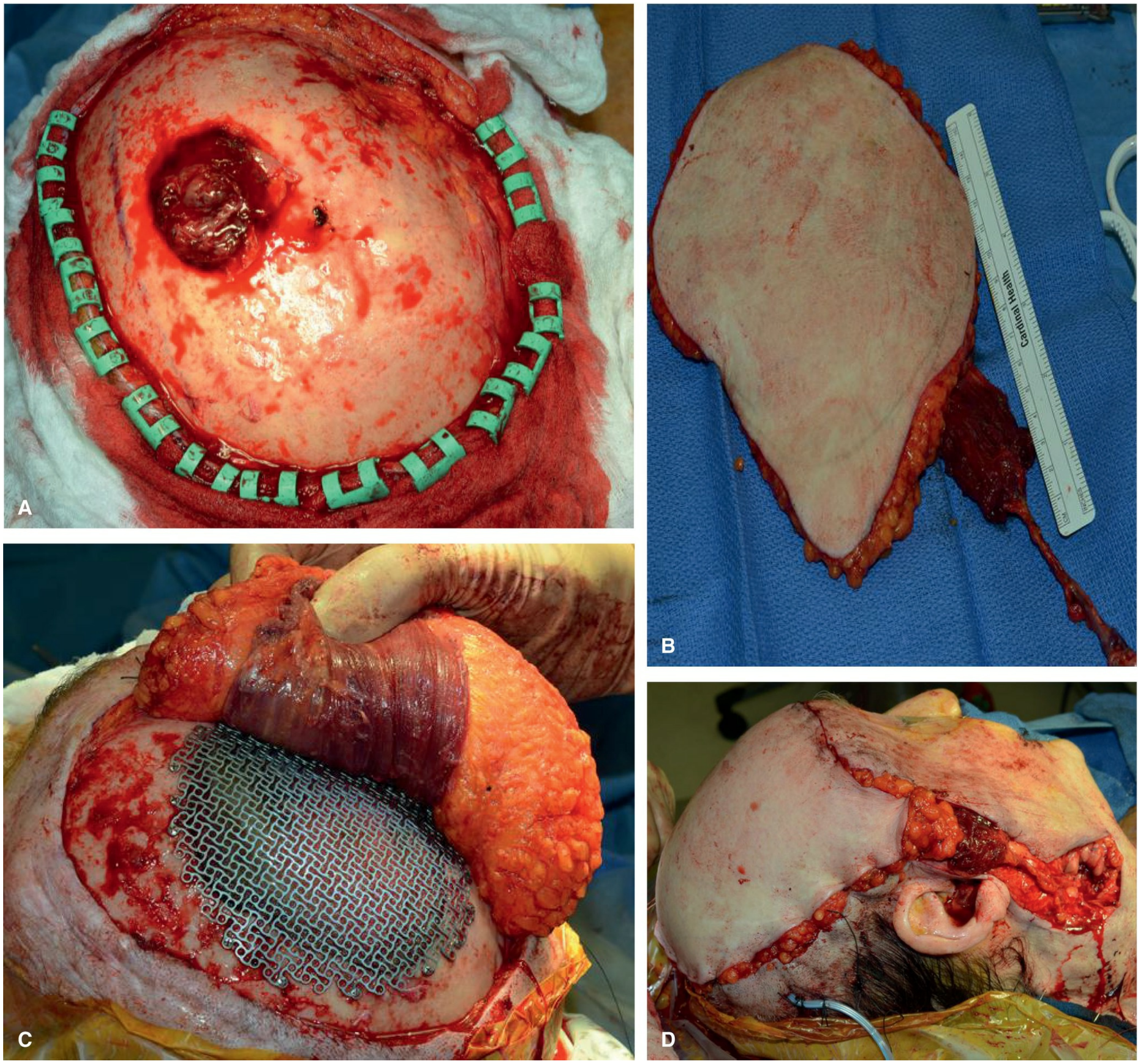


Figure 28.5. A: Large scalp defect with an area of full-thickness skull defect. **B:** Rectus abdominis flap with the deep inferior epigastric vascular pedicle. **C:** The muscle component of the flap is used to cover the mesh reconstruction of the skull defect. **D:** Sufficient skin is available for coverage of a large soft tissue defect. The vascular pedicle is carried through the preauricular incision and anastomosed to vessels in the superior neck.

The major potential disadvantage of the rectus free flap is its excessive bulk, especially in obese patients. This can be corrected by subsequent debulking procedures or by intraoperative modification of the flap's design. An alternative solution is to harvest the muscle alone or in combination with a variable thickness of subcutaneous tissue. A skin graft can be placed to

resurface the muscle if necessary. In any case, postoperative atrophy of the muscle layer should be anticipated.

Gracilis Flap.

The gracilis muscle is a long strap-like muscle that arises from the pubic symphysis and ramus and inserts below the knee onto the fibula. The gracilis muscle is favored by many surgeons who perform free tissue transfer for facial reanimation because the muscle's individual fascicular territories allow the use of smaller muscle units for restoration of specific facial movements. It can also be used as an innervated myocutaneous flap for reconstruction of the tongue or for radical parotidectomy defects when the mimetic facial muscles are resected or cannot be reinnervated.[35,36]

Vascularized Bone-Containing Free Flaps

Vascularized, bone-containing free flaps have revolutionized the reconstruction of segmental mandibular and palatomaxillary defects by reliably restoring continuity of bone and soft tissue in the primary setting. The fibula, iliac crest, and scapula all provide vascularized bone of adequate stock to replace the resected segment. All have advantages, limitations, and donor site morbidities, leading to their use in different circumstances. The most important differences relate to the quality, quantity, and reliability of the soft tissue component of the composite flap. Other essential differences include (1) the potential for osseointegration of the bone component[37,38]; (2) the length and caliber of the vascular pedicle; (3) the ease of positioning, harvesting, and insetting of the flap; and (4) the potential complications and functional deficits associated with the sacrifice of bone and adjacent soft tissue at the donor site.

Fibula Flap.

The principal attribute of the fibula free flap is the exceptional length of bone it provides, making it the only bone-containing free flap that is adequate for total or subtotal mandibular reconstruction.[39] Up to 26 cm of fibula bone can be harvested in the adult male, and the rich periosteal blood supply of the fibula from the peroneal artery allows the creation of multiple wedge-shaped osteotomies for precise contouring of the neomandible or maxilla, without compromise of bone viability (**Fig. 28.6**). It is important that the periosteum

over the bone to be used is not stripped, and thus, the bone and periosteum are cut together when creating osteotomies.[40] The thick bicortical bone accepts osseointegrated implants for dental rehabilitation.[41]

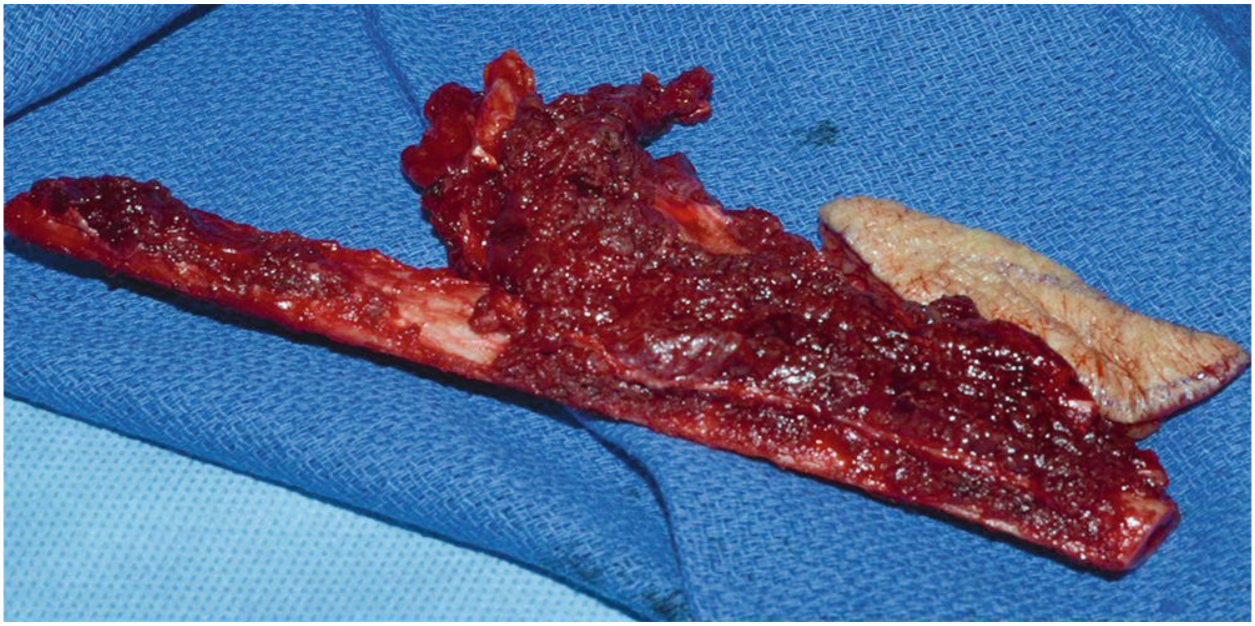


Figure 28.6. Fibula flap harvested. Periosteum is preserved in the distal portion of the flap to ensure viability of the bone.

The peroneal artery supplies the fibula and also gives rise to septocutaneous perforators that run in the posterior crural septum to supply the skin of the lateral calf. Because there are variations in the location of the perforators to the skin paddle, it is best to design a long anterior curvilinear incision that will allow exposure to the intermuscular septal perforators along the entire length of the available bone (**Fig. 28.7**). The posterior incision can then be modified based on the location of the perforator(s) and dimensions of the soft tissue defect.[42]

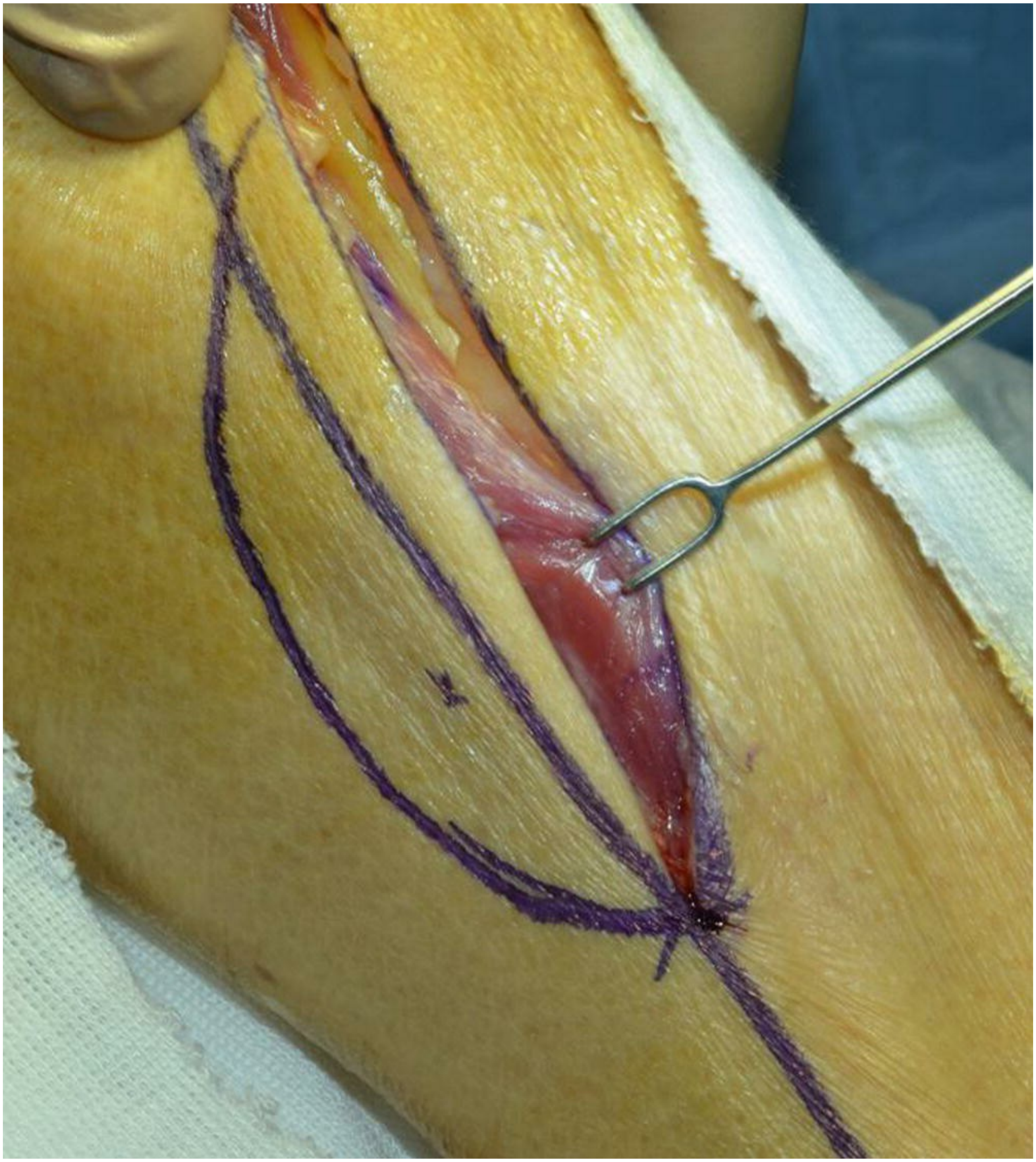


Figure 28.7. Anterior incision is made over peroneus longus and brevis muscle, and the perforator to the skin paddle is located prior to planning the posterior incision.

Advantages include simultaneous two-team harvest with the patient in the supine position. Furthermore, sensory reinnervation of the skin paddle is

possible through incorporation of the lateral sural nerve into the flap design. Due to the quality of the bone and soft tissue, it has been used extensively for palatomaxillary reconstruction.[43]

The main disadvantage of the fibula free flap is the limitation imposed by its soft tissue component. Fasciocutaneous and musculocutaneous perforators of the peroneal artery supply the skin over the lateral calf and permit the harvest of a composite osteocutaneous flap. However, the poor arc of rotation of the skin island relative to bone and its unpredictable pattern of vascularity limit its application to soft tissue reconstruction. Although methods to increase the reliability of the skin paddle have been described,[44] extensive composite oromandibular defects should be reconstructed with an alternative flap, such as the scapula osteocutaneous free flap or the internal oblique–iliac crest composite free flap. Alternatively, a bone-containing free flap can be used in combination with a separate fasciocutaneous free flap or a regional pedicled flap. The presence of atherosclerosis or congenital vascular anomalies of the lower extremity must be identified preoperatively and contraindicate the harvest of the fibula free flap. A preoperative angiogram, CTA or MRA, should be performed to delineate these abnormalities.

The donor site morbidity associated with the fibula osteocutaneous flap is minimal. Two potential complications are injury to the peroneal nerve, which results in foot drop, and instability of the knee or ankle joints. Both of these complications can be avoided provided that the proximal and distal 6 to 8 cm of fibula bone is preserved.

In summary, the osseous and composite osteocutaneous fibula flaps are valuable additions to the available composite flaps used for oromandibular and palatomaxillary reconstruction. The donor site provides the largest length of available bone with limited functional impairment relative to other bone donor sites.

Iliac Crest Flap.

The large amount of bone available from the ileum has made it a popular source for nonvascularized bone grafts, corticocancellous chips as well as vascularized bone transfer. The advantages of the ileum as a donor site are numerous. They include (1) the thick bicortical bone stock, which facilitates dental prosthetic rehabilitation with osseointegrated implants; (2) the ability of the donor site scar to be well hidden by conventional undergarments; and

(3) the ease of flap harvest by a separate surgical team with the patient in a supine position. In addition, the anterior ileum is similar in shape to the native hemimandible. A total of 10 to 16 cm of bone can be harvested, and osteotomies can be made to reconstruct hemimandibular or angle-to-angle defects. Furthermore, depending on the soft tissue needs of the patient, the iliac crest free flap can be harvested as an osseous flap, an osteocutaneous flap, or a tripartite osteomyocutaneous flap when used in combination with the internal oblique muscle. The iliac crest free flap with the internal oblique muscle has been applied to palatomaxillary reconstruction with good results, allowing placement of osseointegrated implants and closure of the palate with the use of the soft tissue components.[45]

The bulkiness, limited pliability, and restricted mobility of the skin paddle relative to the bone, limit the use of the osteocutaneous flap for reconstruction of complex composite defects. Alternatively, the highly mobile, thin, and well-vascularized internal oblique muscle can be used to resurface defects in the oral cavity and pharyngeal mucosa. Similarly, a portion of the muscle can be used to cover the bone graft and reconstruction plate. Skin grafting of the internal oblique muscle is unnecessary because the well-vascularized flap rapidly mucosalizes. The denervated muscle subsequently undergoes atrophy and provides a thin, well-vascularized, and immobile layer of tissue over the mandible.[46]

The iliac crest free flap has been applied to the reconstruction of a variety of defects in the head and neck. The osteocutaneous flap has been used for reconstruction of the anterior mandible in association with total or subtotal glossectomy defects. In this instance, the iliac bone is placed transversely in the floor of the mouth to support the skin paddle, which is used to reconstruct the tongue. Excellent long-term maintenance of the height of the neotongue has been reported with this flap design.[47] The iliac crest free flap has also been used for reconstruction of skull base and maxillectomy defects.[48]

The harvest of the iliac crest free flap involves a considerable amount of dissection. Because most of the lower abdominal wall muscles and part of the inguinal ligament are divided, ventral hernia formation is a significant potential risk. Meticulous closure of the donor site, including the use of mesh for select cases, helps to minimize this risk. The patient experiences postoperative hip pain and weakness, but this generally subsides after several weeks. Despite these potential donor site problems, extensive clinical

experience with the iliac crest free flap has demonstrated its reliability in achieving functional oromandibular reconstruction for even the most complex composite mandibulectomy defects.

Scapular System of Flaps.

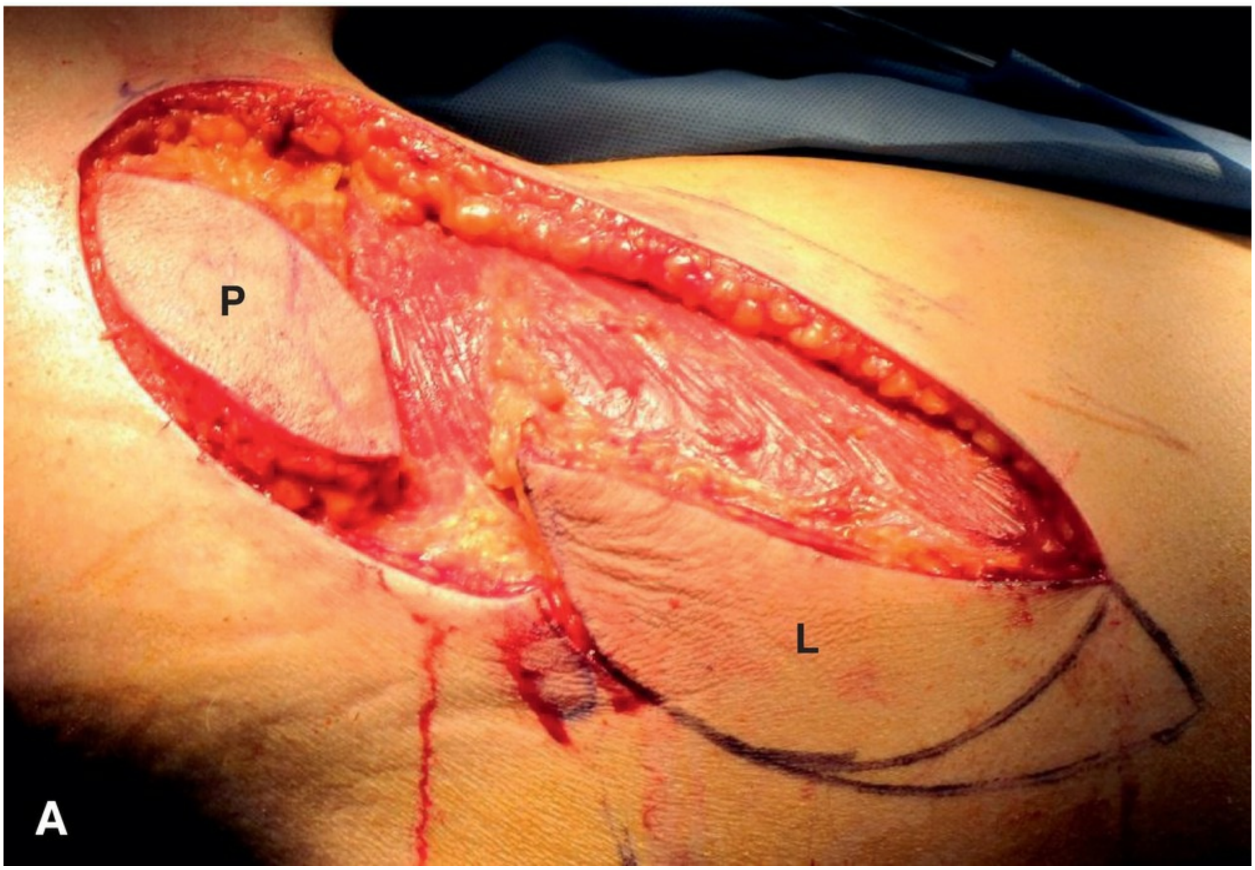
Flaps based on the distal ramifications of the subscapular artery provide a wide array of available tissue for reconstruction of defects in the head and neck. These flaps include the scapular and parascapular fascial or fasciocutaneous free flaps, the lateral or medial scapular osteocutaneous free flaps, the serratus anterior flap, the latissimus dorsi muscle or myocutaneous flap, the latissimus dorsi-rib flap, and the serratus anterior-rib flap.[49]–[52]

After its takeoff from the subscapular artery, the thoracodorsal artery descends along the surface of the serratus muscle for a distance of 9 cm before entering the latissimus dorsi muscle. The latissimus dorsi muscle may be harvested as a pedicled or free muscle flap, a myocutaneous flap, or an osteomyocutaneous flap incorporating a segment of rib. The thoracodorsal artery is consistently accompanied by the thoracodorsal vein and the thoracodorsal nerve, which is the motor nerve to the latissimus dorsi muscle. This neurovascular pedicle has been used to provide reinnervated muscle for total glossectomy reconstruction and facial nerve rehabilitation. It is important to note that the functional advantage of reinnervated muscle in total glossectomy reconstruction has not been demonstrated conclusively.

The angular branch arises from the thoracodorsal vessels or the branch to the serratus anterior and supplies the periosteum of the tip of the scapula. Dissection and inclusion of this branch allows for up to 8 cm of scapular tip to be harvested independently from a separate lateral scapular bone flap based on the circumflex scapular artery. This permits the transfer of two separate scapular bone segments based on a single subscapular vascular pedicle and separated by a 13- to 15-cm arc of rotation.[53]

The scapular system of flaps has been used for a wide variety of reconstructive problems in the head and neck. The scapular and parascapular flaps have been employed as osteocutaneous flaps for reconstruction of oromandibular and orbitomaxillary defects,[54,55] whereas fasciocutaneous flaps have been found to be useful for augmentation of a variety of congenital and acquired facial cutaneous and contour deficiencies.[56]–[58] The latissimus dorsi flap has been used for reconstruction of a wide variety of

oromandibular, pharyngoesophageal, midface, craniotemporal, and craniofacial defects.[59] Several skin, bone, and muscle flaps can be harvested on a single subscapular vascular pedicle, creating the so-called megaflap[60] (**Fig. 28.8**). Up to 875 cm2 of tissue has been reported to be transferred on a single pedicle with the use of this technique. Separate arcs of rotation around the periosteal, transverse cutaneous, and descending cutaneous branches of the circumflex scapular artery and the muscular and angular branches of the thoracodorsal artery provide for extreme flexibility in the use of this flap for reconstruction of extensive and complex defects in the head and neck.[61]



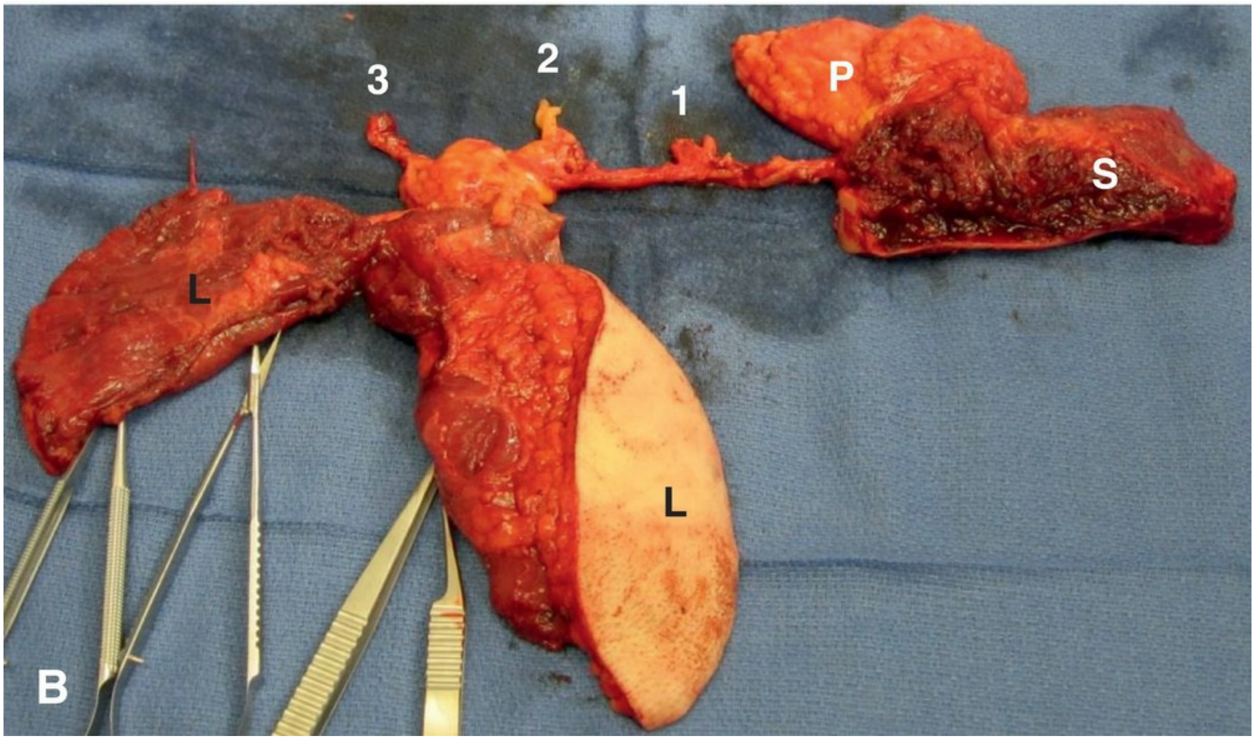


Figure 28.8. Subscapular megaflap. **A:** Multiple skin paddle can be designed. Here, a parascapular (P) skin paddle supplied by the descending cutaneous branch of the circumflex scapular artery and an anterior latissimus dorsi skin (L) paddle supplied by the vertical branch of the thoracodorsal artery are shown. **B:** Multiple components of the flap allow for reconstruction of complex defects. (1, Subscapular artery and vein; 2, angular branch; 3, branch to serratus anterior; P, parascapular skin paddle; S, lateral border of the scapula bone; L, latissimus dorsi muscle divided into two paddles based on the vertical and the transverse branches of the thoracodorsal artery.)

The major disadvantage of the scapular system of flaps is the need for the patient to be in the lateral decubitus surgical position required for flap harvest. This position frequently requires intraoperative repositioning of the patient and precludes simultaneous flap harvest during the ablative portion of the surgery. Both the iliac crest and the fibula provide better bone stock for mandibular reconstruction to support an implant-borne dental prosthesis. Postoperatively, patients should have immobilization of the shoulder for 5 days followed by physical therapy consisting of gradually increased range-of-motion exercises.

Visceral Free Flaps

In cases where thin, pliable tissue is required for immediate reconstruction, visceral free flaps are an option. Jejunum and the greater curvature of the stomach are sources of visceral tissue that have been used as free flaps for upper aerodigestive tract reconstruction, especially for circumferential pharyngoesophageal defects.

Jejunal Free Flap.

The jejunal free flap is a popular technique for reconstruction in patients who require circumferential reconstruction following laryngopharyngectomy with preservation of the cervical esophagus.[62–64]

Superior and inferior enteric anastomoses are performed in an end-to-end fashion. The superior enteric anastomosis between the jejunum and the pharynx is often carried out after the antimesenteric border of the jejunum is incised for a distance of 2 to 4 cm, to enlarge the lumen of the graft and to provide a more suitable size match with the upper resection margin. Exteriorization of a portion of jejunal mucosa allows for postoperative monitoring through assessment of flap color, peristalsis, and the quality of mucosal bleeding. The external monitor is left in place during the first postoperative week, when the risk of flap failure is highest, after which the mesentery to the monitor is divided and the exteriorized segment of jejunum is removed.

Jejunal free flaps have been used after laryngopharyngectomy, esophagectomy with laryngeal preservation, wide-field resection of stomal recurrences, and pharyngoesophagectomy for chronic pharyngoesophagocutaneous fistulae. For noncircumferential defects, jejunal autografts can be opened along the antimesenteric border and used as patch grafts for a wide variety of oral and pharyngeal reconstructions. The potential morbidity of a laparotomy must be balanced against the use of the wide variety of cutaneous flaps outlined above.

Jejunal autografts have several advantages over other methods of pharyngoesophageal reconstruction. Jejunal mucus production is beneficial to patients with xerostomia secondary to previous radiation therapy. Compared with patients undergoing gastric pull-up, perioperative morbidity and mortality are less. Also, jejunal autografts easily reach the oro- and nasopharynx without the excessive anastomotic tension and mucosal ischemia that can occur after gastric pull-up.[65]

Disadvantages of free jejunal autografts are apparent. A successful outcome depends on the results of two microvascular and three enteric anastomoses, which require expertise in both microvascular surgical techniques and gastrointestinal surgery. The inferior pharyngeal anastomosis may be difficult to perform in cases in which tumor extends into the thoracic esophagus. Many authors feel that the peristaltic contractions of transplanted jejunum are not coordinated with the swallowing mechanism and that these contractions may therefore contribute to postoperative dysphagia. However, the motor activity of jejunal autografts decreases over time after transplantation and, functionally, becomes inert conduits. One of the major criticisms of jejunal free flaps has been their failure to enable adequate neoesophageal speech after laryngectomy. However, conflicting reports document successful speech rehabilitation with the use of tracheojejunal fistulas.[66,67]

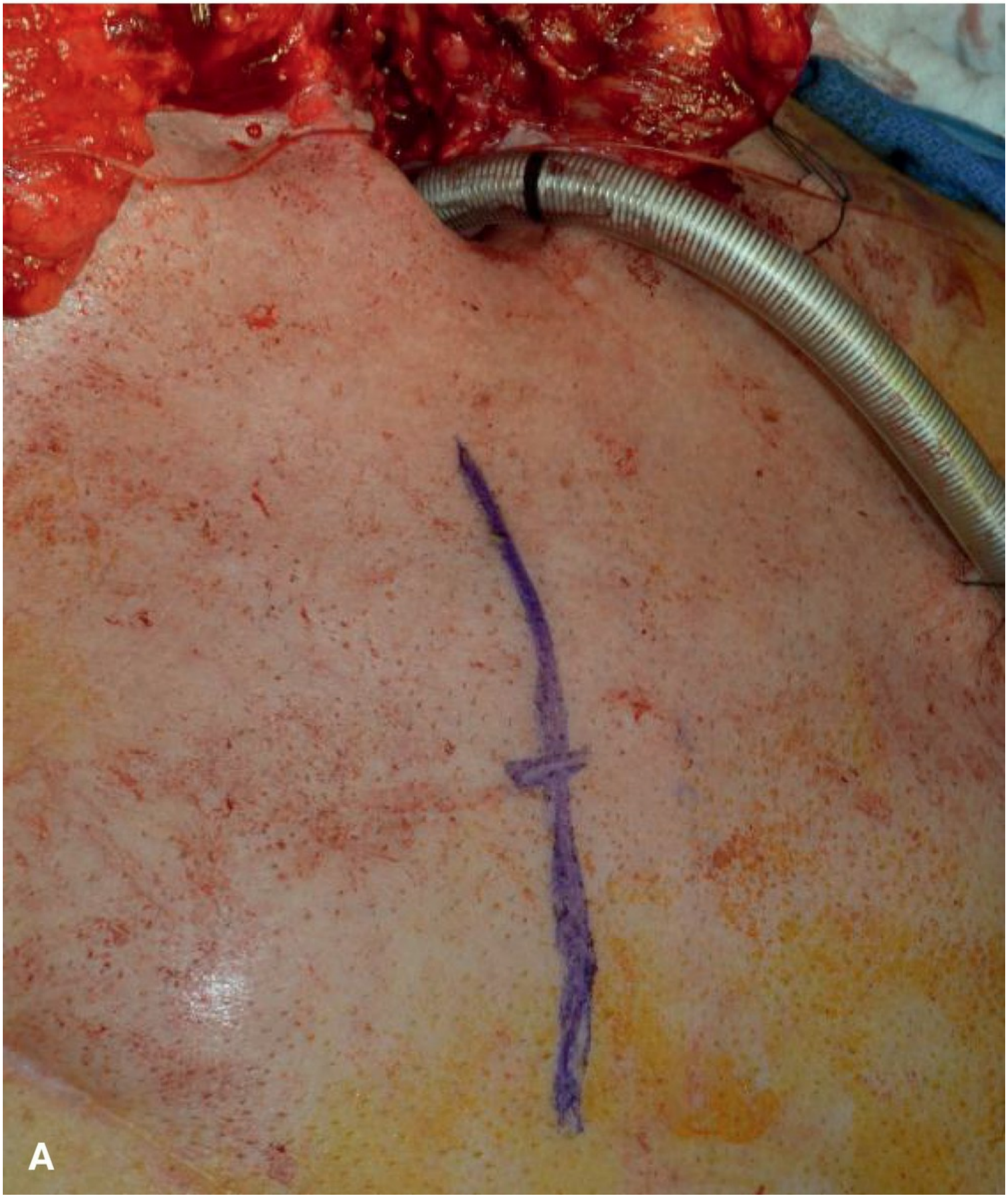
Gastro-omental Free Flap.

Hiebert and Cummings[68] reported the first successful case of pharyngoesophageal reconstruction using a segment of revascularized gastric antrum in 1961. Since that time, the gastro-omental flap has been employed for a variety of reconstructive needs in the head and neck.

The gastro-omental flap is pedicled on the right gastroepiploic artery and vein, which arise from the celiac trunk via the gastroduodenal artery and vein. A 10 × 10-cm segment of gastric mucosa from the greater curvature can be harvested for the purpose of reconstructing pharyngoesophageal mucosal defects. A tubed segment of gastric mucosa can be harvested very rapidly with an enteric stapling device and then opened at each end to achieve a suitable epithelium-lined tube. The greater omentum is frequently harvested with the flap to provide carotid artery protection after concurrent neck dissection or protection of the mediastinal contents when a mediastinal dissection is performed.[69] The inclusion of omentum with the tubed gastric mucosal flap is particularly useful for overcoming impaired wound healing in patients who have undergone previous radiation.

The chief advantage of the gastro-omental flap is that it provides ample pliable soft tissue that closely approximates native pharyngeal mucosa. The long vascular pedicle can reach more remote recipient vessels, including those in the contralateral neck or the internal mammary artery and vein (**Fig.**

28.9). The secretory capacity of the gastric mucosa has been helpful in controlling the symptoms of xerostomia in patients who have received previous radiation therapy. During the first postoperative 7 to 10 days, mucus production is copious, and patients with retained larynges often require airway protection with a cuffed tracheotomy tube. Gastric mucosal rugae quickly flatten after transfer. Omentum contains a rich lymphatic network, and omental transfer has been used to treat various forms of chronic lymphedema, although clinical experience with omental flaps for treatment of lymphedema of the head and neck has been disappointing.[70] Experimental evidence suggests that omentum possesses special qualities that promote the formation of fibrous tissue and capillary ingrowth, as well as hemostasis, making it favorable for reconstruction of previously irradiated or contaminated surgical defects.[71]



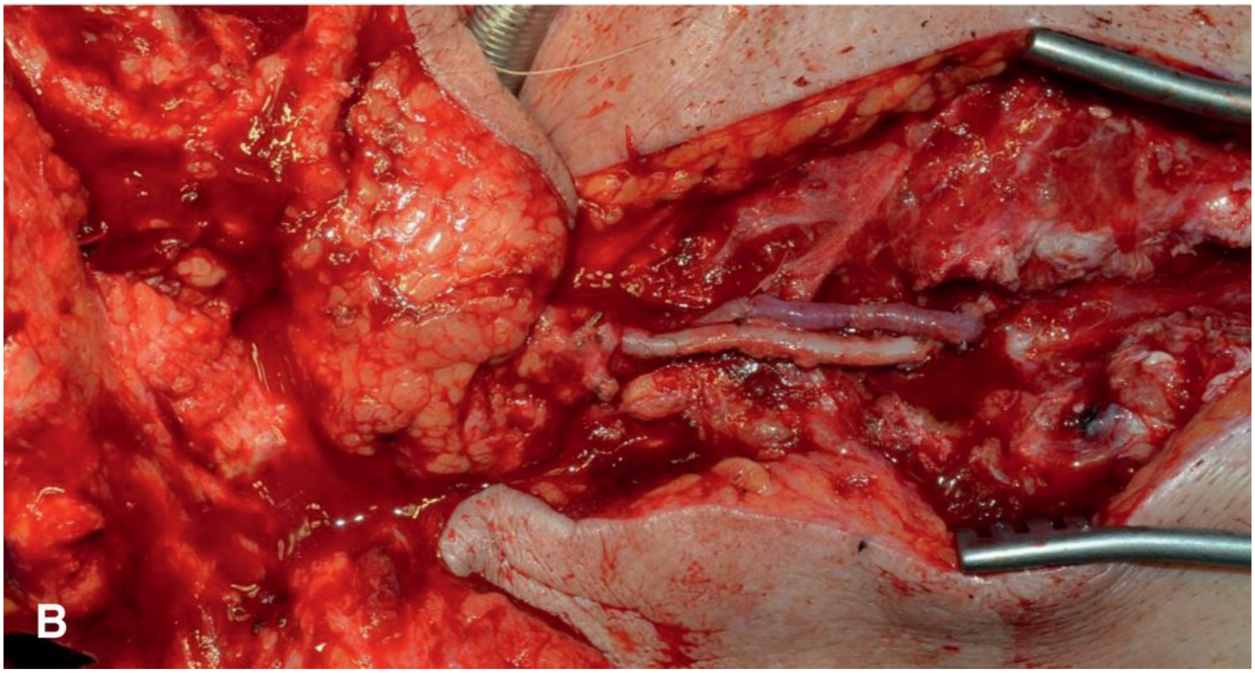


Figure 28.9. Internal mammary artery and vein. **A:** Parasternal incision is planned in order to expose the second and third costal cartilages. **B:** After the removal of the medial aspects of the second and third costal cartilages, the internal mammary artery and vein are exposed, ligated distally, and transposed in a cephalad direction.

Disadvantages of the gastro-omental flap include the need for two surgical teams and the morbidity related to laparotomy. Previous gastric surgery is a contraindication to flap harvest, and adhesions related to previous abdominal surgery or peritonitis may make dissection of the omentum more difficult. Gastrointestinal obstruction is a potential complication and may be caused by pyloric spasm or stenosis, volvulus, or adhesion formation.

OROMANDIBULAR RECONSTRUCTION

The goals of reconstruction following ablative surgery for cancer of the oral cavity are to maintain/restore oral function and to preserve lower facial symmetry. Functional parameters such as articulation, mastication, deglutition, oral competence, and airway protection play a significant role in postoperative quality of life. Despite recent advances in reconstructive surgery, achievement of these goals remains a complex task. The numerous

technical challenges are compounded by the need to operate in a contaminated field that is also at high risk for salivary leak in the immediate postoperative period. It is also made more complex by virtue of the need to package the start of adjuvant postoperative radiation therapy, or combined adjuvant therapy with radiation and chemotherapy, into a 6-week postoperative window.

Classification of composite defects is a critical initial step in achieving a successful reconstruction of the oral cavity. Stratification of these defects should account for the status of bone, soft tissue, and neurologic structures in this region.[72,73] The mandible can be divided into various segments based on a number of factors, including the functional impairment that results from disruption of the muscles of mastication and the suprahyoid muscles that insert into the mandible and participate in laryngeal suspension and elevation. The complexity associated with reconstruction of specific structures, such as the condyle and temporomandibular joint, should also be reflected in the classification scheme.

The classification of soft tissue defects is more complex owing to the highly specialized and dynamic nature of the oral lining and muscles (**Table 28.3**). Because of the critical importance of the tongue in oral function, glossectomy defects should be analyzed carefully. The mobile tongue should be distinguished from the base of the tongue, and the extent of tissue loss should be quantified. Denervated tongue should be distinguished from functional tongue tissue. Adjacent soft tissue defects are defined, including those involving the palate, pharynx, floor of the mouth, lips, and buccal mucosa. External cutaneous defects of the cheek, chin, and neck must also be addressed. Neurologic deficits involving the hypoglossal, lingual, facial, and inferior alveolar nerves must be specified (**Table 28.4**). Although it is always best to try to use a simple classification system, the complexity of the oral anatomy as well as the degree of detail that can be restored to these anatomic regions using modern reconstructive techniques demands an equally detailed description. Furthermore, the condition of the remaining dentition and tissues must be considered. A heavily irradiated or densely scarred recipient bed generally requires well-vascularized tissue for reconstruction.

Table 28.3 Classification of Soft Tissue Defects in the Oral Cavity

Defect	Abbreviation
Mucosa	
Labial	L
Buccal	B
Soft palate	SP
Hemi	SP^{H}
Total	SP^{T}
Floor of mouth	FOM
Anterior	FOM^{a}
Lateral	FOM^{L}
Pharynx	PH
Lateral	PH^{L}
Posterior	PH^{P}
Tongue	
Mobile	
One-quarter	$T^{M}_{1/4}$
One-half	$T^{M}_{1/2}$
Three-quarters	$T^{M}_{3/4}$
Nonfunctional	T^{B}_{NF}
Tongue base	
One-quarter	$T^{B}_{3/4}$
One-half	$T^{B}_{1/2}$
Three-quarters	$T^{B}_{3/4}$
Nonfunctional	T^{B}_{NF}
Total glossectomy	TG
Cutaneous defects	C
Cheek	C^{CH}
Neck	C^{N}
Mentum	C^{M}
Lips	C^{L}
Upper (1/4, 1/2, 3/4, total):	$C^{UL}_{1/4} \cdot C^{UL}_{1/2} \cdot C^{UL}_{3/4} \cdot C^{UL}_{T}$
Lower (1/4, 1/2, 3/4, total):	$C^{LL}_{1/4} \cdot C^{LL}_{1/2} \cdot C^{LL}_{3/4} \cdot C^{LL}_{T}$

Table 28.4 Classification of Neurologic Defects	
Defect	**Abbreviation**
Nerve	
Hypoglossal	N_H
Lingual	N_L
Facial	N_F
Inferior alveolar	N_{IA}
Bilateral defects	N^B

Reconstruction of the Mandible

The number of approaches that have been applied to the restoration of mandibular continuity attests to the complexity of the problem.[74–77] Two major criticisms of mandibular reconstruction in the past were the high failure rate of primary reconstruction using conventional techniques and the inability of patients, whose mandibles were restored, to wear dentures that allowed them to effectively chew. Prior to the availability of vascularized bone grafts, the low success rate of mandibular restoration with free bone grafts and alloplastic materials discouraged primary reconstruction.[78] Avascular mandibular substitutes, which relied on neovascularization and creeping substitution, were prone to infection and extrusion. In contrast, vascularized bone grafts undergo primary healing even in unfavorable recipient beds,[79] and success rate of oromandibular reconstruction using vascularized bone-containing free flaps is now well over 96%.[77] Endosteal dental implants, which function as tooth root analogues, have provided a solution to the problem of denture instability and poor retention. This form of dental rehabilitation can provide superior functional results as documented by the testing of bite force and chewing performance.[80–82]

The fibula, scapula, and iliac crest composite flaps are the most commonly used vascularized bone-containing free flaps for restoration of mandibular continuity.[39,54,77,83–85] Each of these composite flaps differs with respect to (1) the quality and quantity (length and cross-sectional area) of

available bone and soft tissue; (2) the length and caliber of the vascular pedicle; (3) donor site morbidity; and (4) the feasibility of a simultaneous two-team approach. When appropriately applied, all three flaps can achieve predictable bony and soft tissue restoration of complex oral cavity defects. There is no single composite flap that satisfies the needs of all patients. It is therefore essential that the reconstructive surgeon be familiar with all three donor sites to individualize the rehabilitation of each patient. Careful flap selection is important to achieving optimal functional and aesthetic results, with more rapid reintegration of the patient into society.

Soft Tissue Reconstruction

The restoration of tongue function is the most critical factor and the most challenging problem in the rehabilitation of patients with cancer of the oral cavity. A small resection of the mobile tongue may be closed primarily with minimal disturbance of function. When a defect of the tongue extends into the adjacent floor of the mouth, reconstruction with a redundant split-thickness skin graft helps to prevent tethering of the tongue. Local flaps transferred from adjacent buccal, palatal, or lingual mucosa have been used to reconstruct small to medium defects of the tongue. These procedures may, however, result in tethering and reduced mobility of the tongue.

Larger defects that involve at least one-half of the mobile tongue result in a greater degree of oral dysfunction. Patients who have undergone resection of the entire tongue, or who are left with a denervated tongue remnant, have the greatest difficulty with articulation, deglutition, and protection of the airway. For total glossectomy defects, decisions regarding the management of the larynx to prevent overwhelming aspiration are based on a variety of factors, including age, pulmonary reserve, and motivation of the patient. In all cases, it is critical that the mobility of the residual tongue be preserved by the use of transplanted, redundant, thin, pliable tissue and that the reconstruction of the mobile tongue and adjacent defects of the floor of the mouth be compartmentalized to ensure separation of the root of the tongue from the lingual surface of the mandible. The pliability and rich vascularity of the radial forearm flap provide the flexibility in design that makes this flap an ideal source of tissue for customized reconstruction of many defects of the oral cavity.[86] A considerable amount of suprafascial vascularized adipose tissue can also be harvested with the radial forearm flap when bulk is

necessary to achieve contact between the neotongue and the palate, as well as the walls of the pharyngeal chamber. Furthermore, sensation to the skin paddle of the forearm flap can be restored by anastomosis of the antebrachial cutaneous nerves to appropriate recipient nerves in the head and neck.

For mandible-sparing total glossectomy defects, it is desirable to reconstruct the neotongue with sufficient bulk consisting of adipose tissue rather than denervated muscle, with the goal of achieving long-term tongue-to-palate contact. Regional myocutaneous flaps tend to atrophy and sag over time owing to the effects of denervation and gravity on the muscle pedicle. Free myocutaneous flaps, including rectus abdominis and latissimus dorsi flaps, may provide superior long-term results. The muscular component can be directly sutured to the mandible to support the position of the skin paddle and to combat the long-term effects of gravity. Motor reinnervation, achieved with the use of the stump of the hypoglossal nerve, helps to maintain the bulk of the transferred muscle, although meaningful movement of the neotongue has not been adequately documented. Another parameter to consider in the functional reconstruction of total glossectomy defects involves sensory reinnervation to enhance control of the food bolus. Bulkier, sensate fasciocutaneous free flaps, such as lateral thigh, anterolateral thigh, and lateral arm flaps, may be helpful in this regard (**Fig. 28.10**).

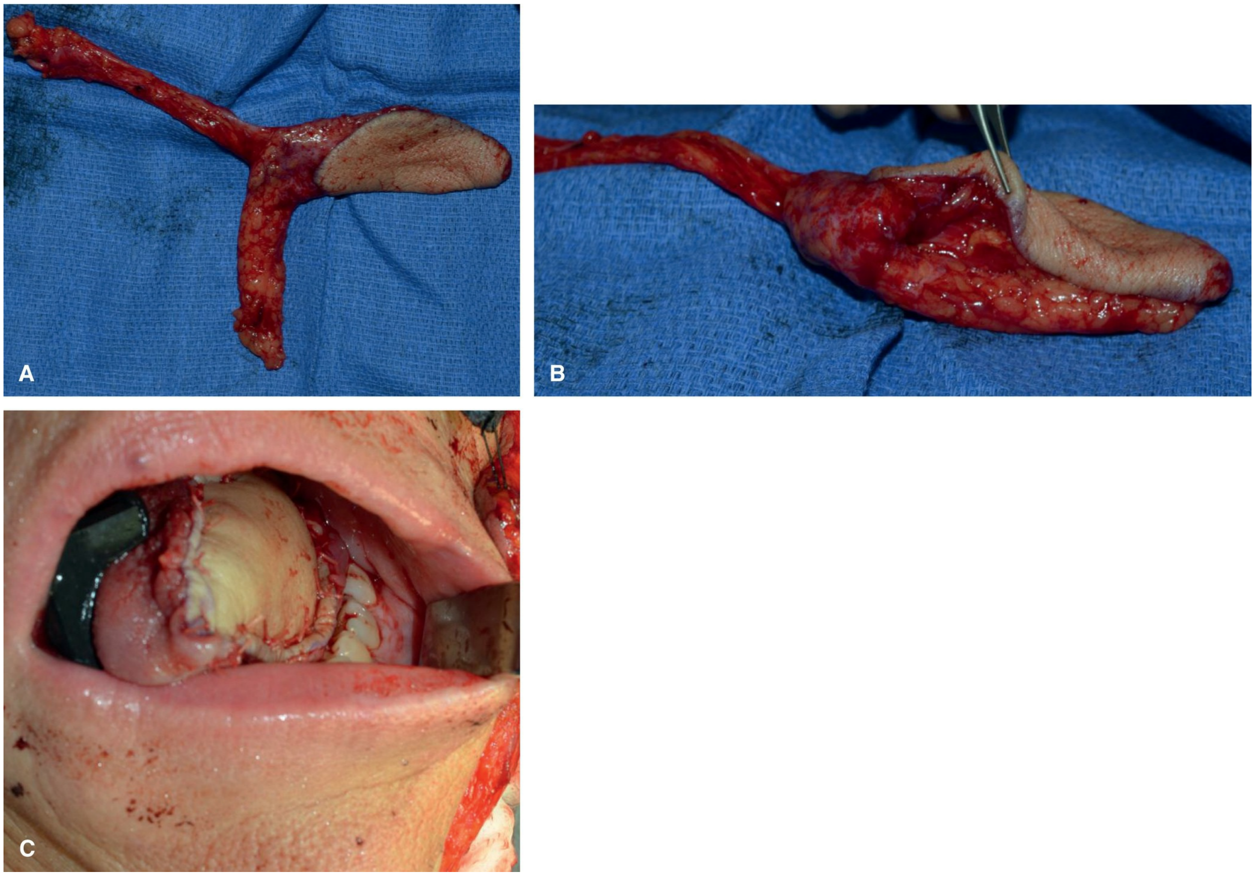


Figure 28.10. A: Radial forearm free flap is harvested with the proximal subcutaneous tissue component (beavertail). **B:** Folding of the beavertail under the distal skin paddle adds volume that may be necessary for functional restoration of a hemiglossectomy defect **(C)**.

A variety of reconstructive options are available for total or near-total glossectomy defects associated with a segmental mandibulectomy. For lateral defects, a mandibular reconstruction plate can be used in conjunction with a soft tissue free flap. However, we have noted an incidence of delayed external plate extrusion with this technique that approaches 30% when patients are followed for longer than 12 months. For reconstruction of anterior mandibulectomy defects, the composite iliac crest flap is inset with the bone in a horizontal position to support the accompanying skin paddle, which is used intraorally to replace the tongue.[87]

For larger or more complex soft tissue defects associated with a segmental mandibulectomy, a single composite free flap may be inadequate to meet reconstructive needs. Only the scapular skin paddle has a sufficient degree of mobility relative to the position of the bone component to allow for

reconstruction of the complex anatomy of the oral cavity (**Fig. 28.11**). However, the scapular skin flap is relatively thick and is not amenable to sensory reinnervation. The skin paddle of the fibula free flap is amenable to sensory reinnervation with the use of the lateral sural cutaneous flap. However, this skin flap has a limited arc of rotation with respect to the underlying bone. The skin paddle of the iliac crest composite flap is excessively bulky for intraoral application in patients with a large body habitus and is not amenable to sensory reinnervation.

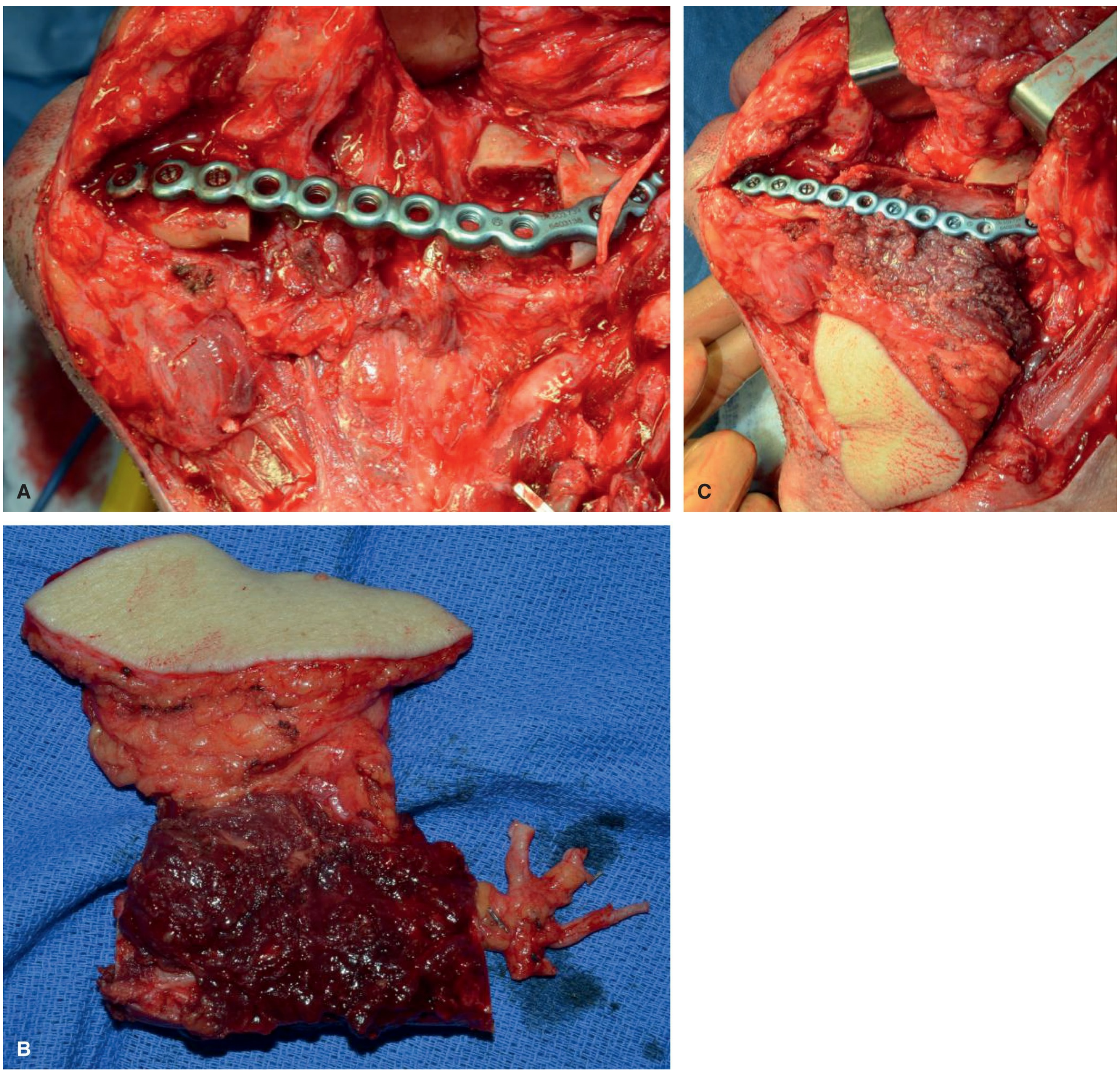


Figure 28.11. A: Segmental mandibular defect reconstructed with a lateral border of the scapula bone. Parascapular skin paddle allows sufficient

mobility around the bone for reconstruction of the intraoral and the external soft tissue defects **(B and C)**.

When a mandibulectomy is performed concurrent with a significant glossectomy, pharyngectomy, or soft palate resection, the radial forearm and lateral arm neurosensory free flaps have been used successfully in conjunction with a vascularized, bone-containing free flap.[88–90] These soft tissue flaps provide the necessary pliability to replicate the native contour of the oral cavity.

Despite reconstructive efforts, virtually all patients who undergo major resection of the oral cavity and oropharynx have some degree of dysarthria, dysphagia, and, sometimes, aspiration. Although many patients are able to compensate, some have prolonged disability. Speech and swallowing therapy is an essential component to maximize the ultimate success of the reconstructive effort.

PALATOMAXILLARY RECONSTRUCTION

As experience in oromandibular reconstruction increased, the transfer of bone-containing composite flaps entered into the mainstream of head and neck surgery. Validation of the functional and aesthetic success in mandibular reconstruction allowed surgeons to turn their attention toward the superior half of the oral cavity and use similar techniques in the functional restoration of palatomaxillary defects.

In many respects, the midface region is a less complicated structure than the oromandibular complex. Most importantly, it is immobile and plays a passive role in mastication and deglutition. Its primary functional role is to provide an opposing surface for the mandible in order to support mastication, as well as a surface to facilitate the tongue’s propulsion of the food bolus during the oral phase of deglutition. The maxillary alveolar ridges support the upper dentition. It also provides the infrastructure for normal midface projection. The three-dimensional shape of the maxilla is somewhat complex, due to the third dimension of the zygomatic bodies, which are in a different plane than the alveolar processes.

The goals of rehabilitation/reconstruction of palatomaxillary defects are to restore the form of the midfacial area while preserving the function of the palatomaxillary complex, which includes the provision of an opposing occlusal surface, support for the globe, and the maintenance/creation of a patent nasal airway. Functional dental rehabilitation is a critical goal that can be achieved through the application of dental implant technology. Numerous techniques, including prosthetic devices, local flaps, regional flaps, and free tissue transfer, have been applied to the restoration of these complex defects.

Palatomaxillary prostheses have been the most popular method of rehabilitation for many palatomaxillary defects. The advantages of prosthetic rehabilitation include a rapid rehabilitation of dentition and return to function, simplification of the surgery, and facilitation of the direct visualization of the surgical site. Biomechanical considerations when the use of a tissue-borne prosthesis is planned include the size of the defect and the number and quality of the remaining dentition for stabilization of the prosthesis. In situations where the remaining maxillary teeth are limited, an osseointegrated implant system is desirable as an alternative solution to fixate the prosthesis. To achieve this goal, the amount and distribution of the remaining alveolar bone are critical factors in determining the feasibility and anticipated success of implant placement. In addition, another very important factor is the radiation status of that remaining bone, which impacts greatly on prognosis for implant success.

Although still the most popular form of restoration of most palatomaxillary defects, prosthetic management has significant drawbacks. Instability of the prosthesis, poor separation of the oral and nasal cavities, patient discomfort, malodor due to stasis of secretions, and daily cleaning and maintenance are genuine concerns associated with prosthetic rehabilitation. Poor hand eye coordination in older patients can make daily prosthetic maintenance a challenging endeavor. Trismus can also be a significant limiting factor that makes prosthetic solutions much more difficult. Consideration of these problems has led to the investigation of alternative methods of rehabilitation. Free tissue transfer has become a reliable method of optimizing rehabilitation of the patient with a palatomaxillary defect.

In 2001, we published a new classification scheme for palatomaxillary defects to provide a framework for communication, treatment planning, and determining the functional prognosis of different restorative/reconstructive

techniques.[91] This system was fundamentally based on the biomechanical properties of the defect with respect to the likelihood for prosthetic success. In that regard, the size of the defect, as well as the number and quality of the remaining dentition, impacts greatly on the different classes. The horizontal component of the defect was determined by the presence of the molars and canine teeth, considered the “pillars” of prosthodontic stability and retention. Class 1a defects were defined as defects of the central hard palate without involvement of the alveolar ridge. Class 1b were defined as either a posterior defect involving one molar, with other remaining pillars of prosthodontic stability in place, or a defect of the anterior premaxilla. Class 2 defects are defined in either the horizontal or vertical plane, whereby at least two of the pillars of stability are preserved. Class 2 defects preserve at least one-half of the hard palate. Larger class 3 defects involve subtotal or total palatal defects wherein either 1 or no pillars are preserved. Subclassification of these defects can be done through designation of the vertical component through designation of additional defects of the zygomatic body(^{z}) and orbital floor (^{f}). Superscripts, which designate the resection of the orbit (^{o}), facial skin (^{s}), and the exposure of the intracranial contents (^{ic}), provide important additional defect classifiers.

Small defects, classes 1a and 1b, that involve the hard palate and a small portion of the tooth-bearing alveolus may be rehabilitated with either a prosthesis or soft tissue reconstruction. Prostheses placed in these defects are usually very stable and well tolerated. However, some patients may have difficulty with the daily prosthetic hygiene required or may simply be unhappy with the effort required to maintain the prosthesis. Numerous techniques for soft tissue reconstruction of this area have been described, including temporalis muscle flaps, buccal mucosal flaps, and the palatal island flap.[10] For reconstruction of small to medium-sized defects of the hard palate and maxillary alveolus, our choice is the palatal island flap[92] (**Fig. 28.12**). In cases of larger defects that cannot be covered effectively by the palatal island flap, or when the patient has had previous irradiation that precludes local tissue transfer, the radial forearm flap provides a reliable and functional closure.[93] Following this type of soft tissue reconstruction, the presence of three pillars of prosthetic retention provides ample support for a conventional tissue-borne prosthesis using clasps as anchors.

Figure 28.12. Palate island rotational flap based on the greater palatine vascular pedicle.

Larger class 2 defects, including the hemipalatectomy defect, are perhaps the most common, and their ideal rehabilitation/reconstruction is controversial.[45,94] Prosthetic management of these defects is challenging, especially in the edentulous patient. The key ingredients for prosthetic stability are the midline palatal shelf and the lateral scar band resulting at the interface of the skin graft and the buccal mucosa. The remaining dental arch and palate may be insufficient to adequately support a prosthetic device, leading to instability and poor separation of the nasal and oral cavities. Free flap soft tissue reconstruction provides an undesirable option for these patients. With only two pillars of prosthetic stability, the placement of soft tissue into this defect eliminates the stabilizing properties of the midline palatal shelf and the lateral scar band. As a result, the patient is actually put at a disadvantage with respect to ultimate dental rehabilitation. Free flap

reconstruction with vascularized bone from the scapula, fibula, and iliac crest has been reported with good results and allows the greatest chance of functional dental restoration with osseointegrated implants. The scapula free flap provides the greatest degree of soft tissue mobility, but the bone stock is often too limited for placement of implants.[94] The fibular free flap provides a large amount of bone that is adequate for implant placement and represents our method of choice when the defect is limited to the horizontal component.[43] Limitations of the fibular composite flap include the limited soft tissue mobility and difficulty in providing adequate form to the orbital rim and zygomatic body when a vertical component exists.

The iliac crest flap with the internal oblique muscle has been extensively described for palatomaxillary reconstruction.[95] The composite flap provides the greatest amount of bone stock for reconstruction of defects with a large vertical component, including the zygoma and the orbital floor. In addition, the internal oblique muscle, with its axial-pattern blood supply in up to 80% of cases, affords the necessary mobility to achieve both palatal and nasal closure. The relatively short vascular pedicle can pose a challenge for flap revascularization. However, cephalad dissection of the facial artery and vein can usually circumvent the necessity for introduction of vein grafts. The latter maneuver must be performed in concert with meticulous dissection and preservation of the marginal mandibular branch of the facial nerve.

Large class 3 defects that include subtotal and total palatal defects are optimally reconstructed with vascularized bone. The ability to contour the fibular flap to match virtually any alveolar ridge defect and to provide the necessary bone for dental rehabilitation with osseointegrated implants makes it a very favorable reconstructive option. In our experience, it is desirable to seal the sinonasal side of the defect as well as the oral side with vascularized soft tissue. To achieve this goal, it is often necessary to introduce a separate vascularized soft tissue flap.

Through application of both regional and free tissue transfers, palatomaxillary defects can be reconstructed in a one-stage technique with very favorable functional and aesthetic outcomes. With the continued increase in the reliability of microvascular free tissue transfer, it is logical to apply it to defects that have been conventionally managed with prosthetic solutions.

PHARYNGOESOPHAGEAL RECONSTRUCTION

Over the past several decades, pharyngoesophageal reconstruction has undergone an evolution from multistaged reconstructions using local tissue as “turn-in flaps” to single-stage reconstructions using free tissue transfer. Simultaneous with this evolution, there was a shift from surgery as the primary form of treatment for cancers of this region to “organ-sparing” therapy with combined chemoradiation. Currently, surgery is often held in reserve for salvage therapy, making it technically more difficult as well as more challenging from a wound healing perspective. The use of healthy, nonirradiated tissue is of paramount importance in order to decrease the likelihood of wound breakdown. With this in mind, the head and neck reconstructive surgeon must have a thorough knowledge of a wide variety of different donor sites, which can be accessed to provide the critical tissue for a successful reconstruction.

In order to best reproduce the pharyngoesophageal segment, one must understand the anatomy, goals of reconstruction, defect characteristics, and potential donor sites. When attempting to reconstruct the pharyngoesophageal segment, the goals can vary depending on the status of the larynx. If the larynx is in place, the reconstruction must center on reconstituting the swallowing conduit and preserving as much sensate mucosa as possible in order to minimize the likelihood of chronic aspiration. The reconstructive goals with an intact larynx are to restore breathing without a tracheostomy, speaking without an artificial prosthesis, and swallowing without aspiration.

Following total laryngectomy, the primary reconstructive goals are to separate the respiratory and digestive tracts, to protect the great vessels from a potential salivary leak, and to prevent a mediastinal infection. Secondary reconstructive goals are to restore pharyngoesophageal function, including rehabilitation of speech and swallowing.

The vast majority of reconstructions are performed in the same setting as the oncologic procedure. However, in certain situations, a diverting pharyngostome is recommended in patients who are at high risk for a salivary leak. In this situation, the final closure of the pharyngostome is performed in a staged fashion.

It is helpful to classify pharyngoesophageal defects for the purpose of treatment planning and determining the prognosis for functional recovery. Disa et al.[96] described a system for classifying the pharyngoesophageal defects in patients following laryngectomy, which was later modified by Urken et al.[97] as follows:

Type 0: small defects of the pharyngoesophageal segment, which are amenable to primary closure. The implication of a type 0 defect is that there is sufficient native mucosa remaining with a favorable blood supply that allows for primary repair without creation of a stricture.

Type I: noncircumferential defects in which a viable strip of mucosa spans the distance between the proximal pharynx and the distal esophagus and measuring a minimum of 2 cm in width. This defect requires a patch-like reconstruction with either a skin or mucosal flap.

Type II: circumferential defects limited to the neck and extending no further cephalad than the level of the vallecula.

Type III: extensive circumferential or noncircumferential loss of mucosa and extending further cephalad than the vallecula.

Type IV: any defect that extends caudal to the level of the clavicles.

Urken further modified Disa's original classification system to include a superscript (^{i}) to indicate that the wound healing is impaired because of prior radiation therapy. This factor was deemed critically important because in this situation, the likelihood of developing a postoperative fistula or stricture is more likely. Urken also modified Disa's classification system to include a superscript (^{s}) to indicate that the defect includes a segment of overlying skin, which requires a flap of skin to be introduced for wound closure.

Methods employed for pharyngoesophageal reconstruction include local skin flaps, regional skin flaps, regional myocutaneous flaps, visceral pedicled flaps (including gastric pull-up and colon transposition), and microvascular free flaps (**Table 28.5**, Pharyngoesophageal Reconstruction).

Table 28.5 Flaps Utilized in Pharyngoesophageal Reconstruction

Local	Cervical Skin
Regional	Deltopectoral Pectoralis major
Visceral pedicled	Gastric pull-up Colon transposition
Free flap	Ulnar forearm Radial forearm Anterolateral thigh Latissimus dorsi Gastro-omental Jejunum Lateral arm

Many patients who undergo a total laryngectomy and partial pharyngectomy have type 0 defects. These patients have enough remaining native mucosa for a primary closure of the alimentary tract without the need to import regional or distant tissue. The disadvantage of this technique is that if there is no sufficient mucosa, these patients are at higher risk of fistula formation and subsequent pharyngoesophageal stenosis. It has been shown that the introduction of nonirradiated tissue can improve wound healing capacity and decrease the likelihood of fistula formation.[98]

Local Skin Flap Reconstruction

Reconstruction of a pharyngoesophageal defect with local skin flaps, similar to the technique described by Wookey,[99] is uncommon in contemporary reconstruction of the head and neck. This technique is best suited for type I and II defects but is reserved for rare circumstances because it requires a multistaged reconstruction, and a single-stage reconstruction is clearly more ideal for patients. This technique is usually reserved for patients who are at high risk to undergo more complex methods of reconstruction because of severe medical comorbidities. Another scenario where a staged reconstruction may be considered is when the ablative surgeon encounters more extensive tumor than anticipated, and the surgeon may not be prepared

to perform a more elaborate reconstruction prior to documenting clear margins on permanent section. Finally, the technique using local skin flaps is often employed when reconstructing a pharyngostome or a mature pharyngocutaneous fistula.

Regional Flap Reconstruction

Reconstruction of the pharyngoesophageal segment with regional tissue is best suited for noncircumferential type I and type II defects. Both the deltopectoral flap and the pectoralis major flap can be used to transfer skin paddles, which can be used to patch a defect in the anterior wall. By transposing skin from the chest wall, one can achieve a single-stage closure when the pharyngeal remnant is too small to close primarily. Regional flaps are less ideal for circumferential defects because of the difficulty of comfortably tubing these flaps because they are not thin or supple.

Type IV pharyngoesophageal defects often require a gastric pull-up in order to replace the cervical and upper thoracic esophagus. For this approach, the surgeon removes the entire esophagus allowing for transposition of the stomach into the cervical region. The advantage of this maneuver is that it allows for a single enteric anastomosis to reduce the risk of fistula formation and avoids an anastomosis in the mediastinum where a fistula can be life threatening.

Free Flap Reconstruction

There are two enteric free flaps commonly used in pharyngoesophageal reconstruction. Jejunal free flaps are usually indicated for type II defects. The advantage of this flap is that it contains secretory gastrointestinal mucosa, and this mucous production may be beneficial to patients with xerostomia. Gastro-omental free flaps are indicated for reconstruction of type II and type III pharyngoesophageal defects. The ability to transfer the omentum, which is a highly vascular and robust tissue, makes this flap a very good choice for through-and-through defects, especially in the radiated setting.

The radial forearm, ulnar flap, lateral arm flap, and anterolateral thigh flap all provide larger surface areas of the skin, which can be used to reconstruct type I, II, or III defects. Each of these flaps has its own intrinsic properties, which may make it more or less preferable as a donor site on a

case-by-case basis.

Reconstruction of the pharyngoesophageal segment has the potential for both short-term and long-term complications. In the postoperative period, a pharyngocutaneous fistula or a major wound breakdown can occur and requires prompt local wound care and possible revision surgery. If a salivary leak occurs and is not recognized, it could lead to a wound infection and leading to the potential erosion of the great vessels resulting in a carotid artery blowout. Therefore, it is vitally important to assess these patients closely during the critical phase of wound healing.

Following the initiation of oral intake, patients can experience difficulties with chronic dysphagia due to an adynamic pharynx. Pharyngoesophageal stenosis may develop as a result of cicatricial scarring, which most commonly occurs at the junction of the pharyngoesophageal segment with the thoracic esophagus. Dynamic barium swallow assessment, using modified barium swallows (MBSs) are an invaluable tool for the evaluation of patients with postoperative dysphagia in order to determine the etiology of a patient’s complaint and a solution to their problem.

FACIAL REANIMATION AFTER MAJOR HEAD AND NECK CANCER RESECTION

Facial paralysis can be a devastating problem for patients following tumor extirpation. Both functional and aesthetic sequelae often lead to isolation, depression, and a limited quality of life. Although the sequelae of ablative and reconstructive surgery for head and neck cancer may leave a patient with deformity of facial and cervical contour and color matched skin, it is asymmetric movement of the face or complete lack of mimetic movement, which immediately catches the human eye and stigmatizes that patient as being “deformed.” Facial reanimation remains one of the most challenging aspects of head and neck reconstruction and requires a patient-specific diagnosis and treatment plan. There are a variety of treatment options from static procedures, local muscle transfers, nerve transfers, and nerve grafts, which all have a role depending on the particular situation. Adjunctive procedures and Botox injection therapy also have important roles in

improving symmetry and overall facial balance. The purpose of this section is to provide a practical framework to construct a sound surgical plan for a patient in the context of their underlying disease.

Consequences of Facial Paralysis and Goals of Reanimation

Complete facial paralysis results in brow ptosis, paralytic ectropion, and loss of smile and lip motion. The most serious consequence is potential blindness related to chronic exposure of the cornea if not addressed early. Chronic epiphora is a common complaint from patients and is caused by overproduction of tears related to corneal dryness as well as impaired lacrimal drainage as a result of the paralyzed orbicularis oculi lacrimal “pump” mechanism. Moisturizing the cornea throughout the day and ensuring eyelid closure at night are part of routine eye care in the management of patients with facial paralysis. Oral incompetence and difficulty with speech and deglutition are also potential problems, as well as loss of superior visual fields related to the descent of the paralyzed brow.

Static eyelid procedures are typically required in the adult population. Children and teenagers generally do not require an eyelid weight or lower lid procedure because passive eye closure and a positive Bell reflex are often adequate given their favorable skin quality. If the iris is visible when the patient closes their eye, damage to the cornea and potential loss of vision may ultimately ensue. A platinum or gold weight is placed deep to the orbicularis oculi muscle to facilitate closure of the upper eyelid. We generally prefer platinum because of its higher density and lower profile.

Lower eyelid malposition with scleral show or full-blown paralytic ectropion needs to be addressed as well. A pre-existing negative cheek vector and delayed lower eyelid snapback test in the setting of facial paralysis can result in profound vision-threatening ectropion. Without muscle tone, midface volume is lost as it descends due to gravitational forces, further compounding the paralytic ectropion because of the loss of cheek support to the lower eyelid. A combination of lower eyelid procedures and restoration of midfacial volume are synergistic in treating lower eyelid malposition. A lower eyelid sling or lid-tightening procedure may be required and is often performed by an oculoplastic surgeon. In salvage cases where vision is in

immediate jeopardy, a formal lateral tarsorrhaphy can provide adequate protection. From an aesthetic standpoint, it is not ideal, but it can be reversed in the future if desired.

Dynamic Versus Static Procedures

Dynamic rehabilitation of the paralyzed face is always preferable to static reconstruction if the patient is an appropriate candidate. Although there are a number of dynamic procedures available, reliability and predictability of reinnervation is a priority in the oncologic patient when life expectancy may be relatively limited. Elderly patients with slow nerve regeneration potential and patients with a poor prognosis or who are in poor health are typically better suited for a static procedure. Although quality of life will be diminished, a static sling can provide symmetry at rest and preserve some degree of oral competence.

The choice of dynamic reconstruction depends on the time of denervation, the status of the target muscles and nerves, and the availability of potential donor nerves. The facial nerve is the only donor nerve that can provide spontaneous facial motion. Panfacial reanimation should be the goal. The ideal situation is found when the patient's native facial musculature is intact and there is a proximal facial nerve, permitting reinnervation to occur. Patients with paralysis for over 2 years are unlikely to have significant functional muscle available due to denervation atrophy. In patients who present <2 years following paralysis, a needle EMG should be obtained to determine the viability of individual facial muscles. If there are fibrillations present, the patient may be a candidate for a nerve transfer or "babysitter procedure".[100] If the EMG is silent, then a free functional muscle transfer can be considered. A young patient with a good prognosis from the underlying disease that led to the paralysis, who can tolerate a 2-year process of facial rehabilitation, is a good candidate for two-stage cross-facial nerve grafting and free muscle transfer if the native muscles are unavailable. However, in older patients, the time for nerve regeneration may be significant. An alternative is to use a free gracilis muscle transfer that receives innervation from the nerve to masseter. This will provide single-stage reanimation in 3 to 6 months, although motion will be strictly voluntary and require the learned process of biting to trigger facial movement. Although the latter is an excellent strategy in younger patients, older patients may find this learned

approach to facial movement to be a challenge.

Immediate Nerve Repair and Nerve Grafting

If the facial nerve can be repaired directly, a tension-free repair is always preferable, typically performed with epineurial sutures using 10-0 nylon suture.[101] If there is any tension on the repair, a nerve graft should be used instead. One common situation is a patient who undergoes radical parotidectomy with preservation of distal facial nerve branches and the proximal facial nerve trunk is intact. If only a portion of the facial nerve is resected, then a nerve graft is a reliable first choice. When the entire facial nerve is resected, nerve grafting to one or two distal nerve targets at most is typically performed. Nerve grafting from the main trunk to all branches is less predictable and may lead to overall weak motor function and considerable synkinesis. In general, we prefer targeting a single distal zygomatic branch that stimulates both smile and lower eyelid motion if this is the sole means for reinnervation. A minihypoglossal transfer can be supplemented to restore lower lip motion and depression to improve symmetry and perioral tone and avoid stretching of the lower lip over time.

The great auricular nerve and the sural nerve are the most commonly used donor nerves for facial nerve interposition grafting.[102] Other donor nerves include branches of the cervical plexus including ansa cervicalis and the medial antebrachial cutaneous nerve. The greater auricular nerve is convenient because it is in the surgical field but has limited length (8 to 10 cm), and the resultant loss of sensation to the earlobe and postauricular region can be bothersome to the patient. The sural nerve is often used because it can be harvested simultaneously and provides greater length (up to 35 cm) than the great auricular nerve. It is located lateral to the Achilles tendon and immediately lateral to the lesser saphenous vein. Sensation to the lateral foot and lower leg are lost following harvest, but this does not typically interfere with gait or strenuous activity. The more proximal portion of the nerve has a smaller caliber and is typically a better size match when performing cross-facial nerve grafts.

The medial antebrachial cutaneous nerve of the forearm is a sensory nerve branch from the medial cord of the brachial plexus and accompanies the basilic vein down the arm before piercing the deep fascia in the middle of the proximal part of the arm. The nerve divides into an anterior and posterior

branch in the distal third of the arm to provide sensation to the anterior medial surface and the posteroulnar surface of the forearm. The donor graft is obtained by making a longitudinal incision in the skin 2 cm anterior and 2 to 3 cm distal to the medial epicondyle. Because of its location in the subcutaneous layer of the forearm, it is a relatively easy and accessible donor nerve to harvest with minimal donor site morbidity.[103] The medial and lateral antebrachial cutaneous nerves can be harvested along with the superficial branch of the radial nerve with a radial forearm free flap, providing vascularized nerve grafting in a previously radiated or hostile environment.[24]

Immediate Nerve Transfers in the Setting of a High Facial Nerve Sacrifice or Absence of a Proximal Facial Nerve Donor

If the proximal facial nerve trunk is unavailable or is intraosseous and far from the distal nerve targets, a combination of nerve grafting and dual nerve transfers can be performed as advocated by Dayan and colleagues.[104] Because time to reinnervation from a high facial nerve injury can take a year or more with unpredictable results, patients who have a limited prognosis would most likely benefit from a nerve to masseter and minihypoglossal transfer, which often provides innervation within 3 to 6 months. These nerve transfers are fairly reliable even in the setting of postoperative or prior radiotherapy. In addition to the dual nerve grafts, a nerve graft from the proximal facial nerve trunk to a distal facial nerve branch targeting both upper and lower portions of the eye sphincter is performed, providing supplemental innervation to the eye sphincter, albeit with a long reinnervation time. The nerve to masseter is transferred to a distal facial nerve branch stimulating both the zygomaticus major muscle (smile) and lower eyelid motion. Finally, a minihypoglossal transfer to the lower lip depressor is performed. This often requires a nerve graft, which is repaired end to side to the hypoglossal nerve following creation of an epineurial window and transection of 30% of the cross-sectional area of the cranial side of the hypoglossal nerve.[100] This provides maximum neural input to the face and minimizes synkinesis because the distal targets and nerve inputs are separate. An upper eyelid platinum weight is also placed in addition to a very modest (5 mm length) lateral tarsorrhaphy, which is not cosmetically

noticeable but provides some degree of lower lid support while the patient is awaiting reinnervation. One of the major benefits of this approach is that the nerve to masseter maintains lower eyelid motion and cheek support with a relatively rapid and reliable reinnervation. In our series, none of these patients required any static lower eyelid procedures for support.[104] This is a significant benefit in terms of quality of life and avoiding the treatment challenges associated with a long-standing paralytic ectropion. Sacrifice of the nerve to masseter is generally well tolerated, as proximal branches can be left intact. However, palpation of the masseter muscle should be performed preoperatively, and consideration should be given to any anticipated sacrifice of the temporalis muscle as loss of both muscles may lead to weakness and asymmetric movement of the lower jaw. Minihypoglossal transfer is also well tolerated, but overaggressive sectioning can lead to dysarthria. Complete sacrifice of the hypoglossal nerve should not be performed. There are alternative nerve donors with a spectrum of advantages and disadvantages including the spinal accessory nerve, phrenic nerve, ansa cervicalis, and nerve to temporalis.

Immediate Muscle Transfer Following Facial Nerve Sacrifice

The benefit of immediate muscle transfer following tumor resection is rapid smile function following the ablation. This is a viable option for patients and may be ideal for those with a poorer prognosis or older patient population. One significant drawback is that muscle transfer for smile does not provide any dynamic rehabilitation to the eye sphincter, which is a priority in facial rehabilitation. We generally favor nerve transfers or grafts to preserve eye sphincter function whenever possible, as long as the waiting time for reinnervation is appropriate given the patient’s disease status.

Muscle transfers including masseter and temporalis transfer have been described, although the vector and outcome of a temporalis muscle transfer is generally preferable. Motion is not spontaneous and requires biting down for smile function. Refinements and modifications of this procedure have been described including a minitemporalis transfer[105] and the Labbe procedure,[106] which in principle is a tendon transfer of the distal temporalis muscle to the oral commissure. Excellent results have been obtained using these techniques.

Free Functioning Muscle Transfer

In patients who underwent resection of the facial musculature or patients who have had facial paralysis for more than 2 years, free functioning muscle will be required. Patient selection is critical in the oncologic population. Patients with a poor prognosis or significant medical comorbidities are clearly not good candidates. There are a number of considerations regarding donor muscle selection and donor nerve selection. Adequate pedicle length, donor site morbidity, and muscle excursion are among the considerations.[107] A variety of muscles have been described including the gracilis, pectoralis minor, latissimus dorsi, serratus anterior, and others. The gracilis muscle is commonly used because of its convenient, rapid harvest, long excursion, and reliable pedicle. The pectoralis minor muscle has advantages in the pediatric population with dual innervation and the potential for multiple vectors of motion.[108] Latissimus dorsi provides ample pedicle length and caliber, but is generally bulky.

The patient's smile vector is evaluated and marked preoperatively and simulated on the contralateral side. Depending on the smile, distal insertion of the muscle is typically along the base of the nasal ala, nasolabial fold, modiolus, and sometimes the lower lip. Inset of the muscle is performed prior to anastomosis and neurorrhaphy as this will determine the final position of the neuromuscular pedicle. Zuker and Manktelow[109] typically debulk the gracilis muscle with the proximal end of the muscle secured to the deep temporal fascia, superior to the zygoma to allow for adequate excursion. One consideration following oncologic resection is that skin coverage may be thin and adherence to the overlying muscle transfer can be unsightly. The gracilis can be harvested with an overlying layer of vascularized adipose tissue to provide a more supple appearance.

Nerve donor selection is an important consideration. The facial nerve is always preferable, when available, for achieving spontaneous motion. If the proximal facial nerve stump is available, it can be used, but plugging into the main trunk of the facial nerve will likely result in excessive contraction. A distal facial nerve branch or smaller nerve graft from the main trunk can be considered. Alternatively, cross-facial nerve grafting in the first stage with free muscle transfer 9 to 12 months later is a good option for a young, motivated patient with a good prognosis. At least two cross-facial nerve

grafts are typically used for eye closure and smile, with other grafts for lower lip depression if desired.[110] A positive Tinel sign can be traced during repopulation of the cross-facial nerve graft as it progresses toward the paralyzed side. Its presence does not predict function, and cross-facial nerve grafts are generally less powerful and less reliable than local nerve transfers. If there is a question of viability of the nerve graft at the time of muscle transfer, a biopsy of the nerve graft can be performed intraoperatively to confirm the presence of healthy fascicles versus fibrotic unusable nerve graft. Nerve to masseter transfer can be discussed with the patient ahead of time and used as a backup.

In patients who are not candidates for a cross-facial nerve graft, or who prefer a single stage with greater power and predictability at the expense of no spontaneous motion, a nerve to masseter is a good alternative. Reinnervation is rapid and donor site morbidity is minimal.

Adjunctive Treatments

There are a number of adjuncts to improve the overall aesthetic and dynamic appearance following oncologic treatment. Loss of volume following resection and radiation can be successfully treated with structural grafting using adipose tissue.[111] This provides a more supple and symmetric appearance particularly following radiotherapy. Botox is commonly used on the nonparalyzed side to achieve improved dynamic symmetry and minimize the discrepancy in motion between the paralyzed and nonparalyzed side. A brow lift is typically required when complete paralysis is present. In older patients who scar well (at least 60 years old, preferably 70), a direct brow lift is very effective. Although endoscopic brow lift is appropriate in certain patients, it should be avoided in those with a high forehead as this will be accentuated following the procedure, and further lifting will generally need to be repeated in the future. Patients with a high forehead are best suited with a brow lift using a pretrichial incision, although numbness of the scalp will occur. Patients who have lost lower lip innervation may develop an elongated and atonic lower lip and require wedge resection to improve oral competence. Physical therapy is an important component of facial rehabilitation of synkinesis or when nerve transfers are used. Synkinesis can be minimized with proper therapy and Botox; and surgical management may be appropriate in certain circumstances, although this is beyond the scope of this chapter.

In conclusion, there is a wide array of techniques available for facial reanimation, and careful selection among them must be made in the context of the patient's disease, goals, and clinical presentation and is critical to a successful outcome. It is also critical to appropriately manage a patient's expectations in order to make certain that return to normalcy is not anticipated and to ensure that the patient and their family are not disappointed with a less than perfect result.

IMPLANT REHABILITATION AND MAXILLOMANDIBULAR FREE FLAP RECONSTRUCTION

Contemporary management of the patient with cancer of the head and neck integrates surgical reconstructive techniques with prosthetic rehabilitation in order to optimize function and aesthetics.[82,112,113] The complexity of vascularized bone free flap reconstruction of maxillomandibular defects necessitates treatment strategies that meet patient expectations in terms of their function, aesthetic, psychological, and social concerns. Edentulous cancer patients who do not achieve oral rehabilitation after cancer surgery can exhibit significant psychological challenges.[114] New approaches to maxillomandibular defects effectively provide a more conventional setting for prosthetic reconstruction of the dentoalveolar arch and surrounding structures. Composite free flaps from the fibula, iliac crest, and scapula regions address both the bone defects as well as the soft tissue requirements to restore the oral cavity, as well as the midface region.[39,45,61,115] Preservation of tongue motion and the restoration of tongue volume are critical in obtaining a favorable functional outcome if tumor extension involves a significant portion of the tongue or floor of the mouth.[95] Vascularized bone-containing free flaps (VBFF) can be used to restore continuity defects of the mandible or reproduce the stable base of the maxilla. Vascularized bone flaps from the fibula or iliac crest donor sites provide vascularized bone required for the use of osseointegration to enhance prosthetic rehabilitation. Composite free flaps from the scapula region are selected when the soft tissue requirements of the defect are significant or when the use of the fibular donor site is contraindicated due to the poor

vascular runoff in the lower extremity or advanced age of the patient. However, the scapular flap has a comparatively poor bone volume for osseointegration. Despite this anatomic limitation, it is often possible to place two to four implants into the scapular bone, probably not more than 10 mm in length, for support of a removable prosthesis.[38,73]

The fact that a bone-containing free flap brings its own blood supply presents additional strategies for implant-assisted prosthetic rehabilitation of acquired defects resulting from the treatment of large benign and malignant tumors of the jaws. The rich vascularity of the transferred bone provides a substrate for osseointegration allowing implant placement prior to the delivery of adjuvant radiation therapy. Placement of implants at the time of the initial reconstructive procedure shortens the overall treatment time to achieve prosthetic restoration. Following primary placement of implants, the restorative team must allow 12 to 16 weeks for undisturbed healing and osseointegration of the fixtures.[116] Once the patient completes radiation therapy and the soft tissue reaction from the radiation treatment has subsided, the fixtures are uncovered. At that time, soft tissue modification such as flap debulking or vestibuloplasty procedures can also be performed. A surgical stent can be used and secured to the implants for healing purposes prior to the fabrication of the definitive prosthesis. The surgical stent can be made with or without teeth depending on the clinical situation and the desire of the patient. The stent promotes undisturbed healing, maintains vestibular height, and improves the function and appearance of the lips and mouth.

Primary implant placement is key in developing a comprehensive approach to ablative surgery, subsequent reconstruction, and prosthodontic rehabilitation with adjunctive radiation. This also holds true for placement of implants into native bone at the time of tumor resection to optimize prosthetic rehabilitation without any additional surgical reconstructive procedures. Primary placement of implants can circumvent the need for hyperbaric oxygen prior to secondary placement of fixtures in patients who receive radiation therapy following their reconstruction.[81] In addition, primary placement of implants minimizes time with an unstable prosthesis and compromised function in the edentulous patient. We reported an 86% rate of success of implants placed into VBFF in the primary setting who were subsequently radiated (n = 81 implants).[117]

If a patient has received irradiation to the head and neck region, it is

important to review the simulation plan, including dosimetry and fields, to determine whether native bone or the VBFF has been adversely affected, resulting in a compromised situation for osseointegration. Patients who undergo hyperbaric oxygen protocol[118,119] do so to enhance the vascularity of the surgical bed prior to implant surgery. Hyperbaric oxygen has been reported to be beneficial to postradiated native mandible[120,121] and fibula free flaps.[122,123]

The decision for fixed versus removable prosthetic restorations is dependent upon clinical factors such as bone availability, the number and position of implants to assist or support the restoration, maintenance of hygiene, and manual dexterity of the patient. In addition to these clinical factors, other comfort and psychosocial considerations will also affect prosthetic design. When addressing the reconstruction of the dental arch with osseointegrated fixtures, our preference is to provide patients with a fixed implant-supported restoration. In cases where the remaining arch is edentulous and where a lateral mandibular free flap reconstruction is performed, the fixtures should be placed in the anterior native mandible. This is an ideal location for implant placement in patients undergoing lateral jaw resection for posterior alveolar or floor of mouth/lateral tongue or tonsillar primary tumors because this area is usually spared of radiation. To minimize cantilever forces of the distal extension of the prosthesis, it is advisable to place a minimum of four or five implants with the greatest anterior–posterior spread to restore the total dental arch. Posterior placement of the distal implant on the contralateral side of the mandible is potentially limited by the inferior alveolar neurovascular bundle and mental nerve. Three to four implants placed into VBFF are recommended for unilateral maxillomandibular defects. As the defect crosses the midline, more implants are necessary to support the prosthesis requiring up to six implants to support a fixed restoration.[124]

There are also issues of peri-implant soft tissue maintenance. When muscle from the free flap is used for lining the oral cavity, the neomucosa around the implants might require repeated surgical debridement of hyperplastic inflammatory tissue around the transmucosal abutments. This problem may require excision and simple repair or possible split-thickness skin grafting (STSG) if there is repeated robust growth of this unwanted tissue.

The advantages of the fibula free flap have made this a “workhorse” flap for mandibular reconstruction. The length of the bone that can be harvested allows for near-total mandibular reconstruction (from condyle to condyle). There is good to excellent bone stock for osseointegration. The bicortical nature of the fibula offers ~12 to 15 mm of bone height for endosteal implant placement.[37] Unlike the scapula or iliac crest free flaps, which are monocortical, implants placed into the fibula should engage both cortices to improve initial stability, osseointegration, and the longer-term ability to resist masticatory forces.[125]

The fibula is tubular and triangular in cross section and the three surfaces have dedicated characteristics. One surface has cutaneous perforators arising from the peroneal artery and vein, the vascular pedicle runs along another surface, and the lateral aspect is used for internal fixation hardware that will secure the flap in position to allow for undisturbed bone healing. The orientation of the skin paddle will determine whether the base or apex of the triangle is oriented as the neoridge of the maxilla or mandible.[42] These factors have significant implications as to whether implants can be placed in the immediate setting, at the time of the surgical reconstruction.

The use of the fibula can present a geometric challenge for prosthetic reconstruction. The fibula is best positioned at the inferior border of the mandible to reproduce contours of the lower third of the face. This may lead to an intraoral alveolar height discrepancy with the native mandible. Additionally, because the alveolus is naturally positioned lingual to the inferior mandibular border, the fibula will be positioned such that implants will be facial to the dentition in the opposing arch. In such cases, an implant-assisted removable overdenture can be constructed so that lip and cheek support and oral competence are promoted. The use of a bar framework positioned lingual to implants can overcome the height discrepancy and facial position. The contours of the mandibular prosthesis can provide support to the lower lip to restore projection and symmetry to the lower face. The loss of motor function from injury of the marginal mandibular branch of the facial nerve can be ameliorated with this means of lip support.

A critical step to optimal functional rehabilitation involves the restoration of bilateral occlusal contacts, where occlusal guidance and protection schemes are restored to that of a fully dentate individual. The position of the mandible is determined by both condylar elements and dental occlusion.

Reconstruction of the mandibular discontinuity defect with a VBFF allows for both condylar determinants to function normally. The status of the occlusion and dentition will have a significant effect on function. Rehabilitation with a fixed dental prosthesis (FDP) provides better results for functional mastication and facial aesthetics as well as less discomfort and psychological disability than removable of prosthetic counterparts.[126–129] These restorations are screw retained, allowing the prosthesis to be retrievable as opposed to a cemented restoration. This design facilitates surveillance of the soft tissue beneath the denture.

Treatment planning should involve the placement of more implants rather than a minimum number for support of a fixed restoration. In the event of an implant failure, prosthetic success is still achievable with a shorter restoration of the dental arch or an implant-assisted overdenture.

Other approaches have been used to overcome the height discrepancy of the fibula free flap relative to the native mandible. One is to position the fibula more superiorly and use the reconstruction plating system to reproduce contours of the inferior border. Another is the “double-barrel” technique where the fibula is folded to increase the height of the bone and reduce the discrepancy between the occlusal plane and reconstruction.[130,131]

The significant height discrepancy of the fibula to the occlusal plane can be overcome by employing a cast mesostructure–superstructure design for a screw-retained fixed restoration. The mesostructure is milled so that the implant support is centralized over the mandibular neoridge and the corresponding superstructure acts as a fixed partial denture set with screws into the mesostructure. This type of prosthetic restoration allows the significant height discrepancy from the implant head to the occlusal plane to be mitigated by two corresponding milled framework structures. Prosthodontic framework design, with the use of computer-assisted planning, improves predictability for implant rehabilitation after VBFF surgical reconstruction. Implant position and angulation is determined from computer tomography (CT) scans where tooth position is visualized.

Computer-assisted planning (CP) is a novel technologic addition to surgical reconstruction and implant placement. We consider its application routinely for patients with VBFF surgical reconstruction of maxillomandibular defects. In the absence of postoperative radiation, secondary placement of implants with CP is an approach that adds accuracy

and facilitates rapid prosthodontic rehabilitation, within 4 to 6 weeks following VBFF reconstruction. One of the additional benefits of computer planning is the ability to place implants in a way that avoids the screws associated with rigid fixation. Alternatively, the decision can be made to remove internal fixation hardware that may interfere with the placement of a sufficient number of implants for a fixed restoration. In this situation, implant surgery is performed once bony union of the VBFF osteotomies is established, ~6 to 8 weeks after surgical reconstruction. We reported a retrospective case series (n = 28 patients) in which computer-aided design and computer-aided manufacturing (CAD–CAM) were employed. The inclusion criteria were patients who underwent VBFF reconstruction and computer-assisted planning for FDP restoration in preparation for implant surgery. Implant success, with immediate load (IL), as well as provisional and definitive FDP restorations in VBFF, was reported for the first time in a patient cohort.[132] Patients were evaluated for implant success; CT-derived surgical templates, immediate provisional restorations, and prosthodontic framework design.

Ninety-nine osseointegrated implants, of the 116 implants placed, were used for prosthetic restorations achieving an 85.4% success rate. One hundred and two implants achieved osseointegration (87.1%). Twenty-five of 28 patients (89.3%) received definitive implant-supported FDP restorations. Two patients received removable implant-assisted restorations, and one patient was unable to complete rehabilitation due to implant failure. Thirteen (13) of 28 patients received immediate or early-loaded fixed restorations at the time of stage I implant surgery. The success rate for implants that were placed in the immediate restoration group was 89.3% (50/56). All 13 patients with immediate restorations had CT-derived surgical templates for their implant surgeries. Twelve of 13 immediate restorations were successful.[132] Computer-assisted implant rehabilitation may enhance the chances for functional recovery for patients who undergo maxillomandibular reconstruction with VBFF. Although overall treatment time may be similar to those patients without immediate restorations, this approach is justified based on the potential to provide patients with fixed provisional restorations during the time for osseointegration and definitive FDP fabrication.[132]

Dental Implantation in Palatomaxillary Reconstruction

Obturators can provide a safe and effective way to successfully restore maxillectomy defects and remain a standard to maxillofacial prosthetic rehabilitation. There are shortcomings though to functional recovery. As defects become larger, nasal escape can compromise speech and swallowing. These side effects also have implications on patient comfort and psychosocial interaction, making surgical reconstruction of palatomaxillary defects a more comprehensive and ideal approach to achieve optimal functional rehabilitation.[133,134]

The use of vascularized free bone flaps to reconstruct large palatomaxillary defects achieves surgical closure and restores the alveolar defect as well as providing a platform for the placement of osseointegrated fixtures.

Our classification system essentially addresses size and location of palatomaxillary defects and considers the biomechanical properties that contribute to prosthetic instability and compromised function.[91] As noted in the discussion above on palatomaxillary reconstruction, larger defects lend themselves to the introduction of VBFFs to provide palatal closure and favorable bone for implant placement. In the event that a fibula is used, the bone should not be used for final projection and support of the lip and mouth. That role is given to the definitive prosthesis and tooth replacement. VBFF plating to the nasomaxillary buttress is positioned just beneath the anterior nasal spine, the pyriform aperture, and the nasal sill. The maxillary anterior teeth are facial to this plane, such that implant placement would then be favorable for a prosthetic restoration. However, there is a tendency for bone availability to be more lateral as the reconstruction moves posterior toward the zygoma. This may lead to implants that are placed in a position that is facial to the dental arch, surrounded by movable cheek mucosa, becoming poor candidates for prosthetic rehabilitation. CP with a radiographic scanning appliance can improve implant position to overcome this relationship. Vascularized bone offers the ability to re-establish the bony dental arch for the placement of osseointegrated implants, which allows for the distribution of masticatory forces across an intact maxillary arch. Surgical reconstruction with fibular or iliac crest free flaps and implant-supported fixed dental prostheses replace analogous structures of a stable palatomaxillary complex. An FDP restoration for a class II defect reconstructed with VBFF leaves remaining sensate palatal mucosa exposed over the tongue promoting

lingual–palatal feedback during function. Furthermore, the VBFF permits the primary reconstruction of the orbital rim and the prominence of the zygomatic body with autologous tissue.[135]

A class III defect extends beyond the midline, involving both canines and ipsilateral molar dentition resulting in a bilateral defect with poor prosthodontic prognosis and severely compromised speech and swallowing. Class III defects are best restored with a VBFF, patient factors not withstanding. As a maxillectomy defect increases in size and the remaining dentition and palate decreases in size, a VBFF is clearly preferred over a fasciocutaneous or musculocutaneous free flap for functional recovery. VBFF reconstruction, osseointegration, and an FDP can restore stable dentoalveolar structures and occlusal contacts to optimize speech and swallowing functions.

SPEECH AND SWALLOWING ASSESSMENT

Evaluation of the patient’s voice, speech, and swallow functioning pre- and post treatment is critical to accurately define functioning at baseline and at periodic intervals after treatment of head and neck cancer. The evaluation should include a thorough assessment of vocal tract functioning, a clinical and instrumental assessment of swallowing, a determination of overall performance status, and administration of patient-rated quality of life (QOL) scales to assess patient QOL. In order to track change in function over time and better predict function with treatment, assessments should be conducted at defined periodic timepoints, including pre- and post treatment (i.e., 1, 3, 6, 12, 24, 36 months post treatment).[136,137] Specified evaluation timepoints enhance the ability to define function over time within patients as well as comparisons between patients undergoing similar or different treatment modalities.

The functional assessment should include a clinical identification and severity rating of any speech, voice, resonance, loudness, rate, or breath support impairment during conversational speech. A thorough oral mechanism examination, with assessment of the lip, tongue, palate, larynx, and jaw range, rate, coordination, and strength of motion for isolated and rapidly repeated/alternated nonspeech and speech tasks. Symmetry and

accuracy of motion should be examined. Surgical interventions should be identified with the intraoral examination, with identification of microvascular flap reconstructions and potential impact on function. Range of motion should be measured for lingual tasks including protrusion and lateral motion, and jaw opening should be measured using the TheraBite measuring disc.[138,139] We have developed a novel tongue ROM measuring system to quantify lingual mobility in the surgically treated partial glossectomy patient. This system takes into account lingual protrusion, lateral motion to the commissures, and lingual elevation to the upper alveolar ridge.[139] Lingual strength should be assessed using a manometric measure, such as the Iowa Oral Performance Instrument (IOPI) or tongue bulbs via the Kay-Pentax Swallow Station.[136,140] Salivary production should be measured, particularly if the patient is to undergo and/or has undergone adjuvant irradiation or chemoradiotherapy. The Saxon test is a simple measurement tool whereby the patient chews on a dry 4 × 4 gauze, which is weighed dry and after 2 minutes of chewing.[141] Laryngeal function testing should include clinical assessment of laryngeal function for phonation, cough, and throat clearing, as well as formal acoustic analysis of variables such as fundamental frequency for speech (F0), absolute intensity, pitch and intensity perturbation measures, signal-to-noise and noise-to-harmonic ratios, and maximum pitch range. Respiratory function testing for phonation should include maximum phonation times for sustained /a/ following normal and deep inhalation and well as loudness testing. Resonance testing should be performed particularly with individuals undergoing hard and soft palate resection. This assessment can include nasality testing utilizing a Nasometer or aerodynamic assessment of nasal/oral airflow during phonation utilizing devices such as the Rothenberg mask.[142,143] Oral function testing should also include examination of one- and two-point discrimination for the lips and tongue, as well as assessment of taste sensitivity.[86,144,145]

Performance status should be assessed with reliable and validated tools, such as the Performance Status Scale that examines diet type (i.e., Normalcy of Diet domain), speech understandability (i.e., Understandability of Speech domain) and impact of surgery on ability to eat socially (i.e., Eating in Public domain).[146,147] Clinician-rated voice scales include the grade, rough, breathy, asthenic, strained (GRBAS) scale and the CAPE-V.[148–150] The Karnofsky Performance Scale, a clinician-rated scale of overall functional impairment,

can also be administered.[151]

Patient-rated QOL scales should be administered to establish a baseline and examine the effects of treatment on patient-rated QOL, including speech, voice, swallowing, and overall head and neck QOL. Reliable and validated voice and speech QOL tools include the Speech Handicap Index, the Voice Handicap Index, VHI-10, and Voice-Related QOL.[152–156] There are many swallowing QOL scales, such as the SWAL-QOL, EAT-10, MD Anderson Dysphagia Inventory, University of Washington Quality of Life Instrument, Vanderbilt Head and Neck Symptom Survey, and Head and Neck Cancer Inventory that are patient-rated symptom-specific scales.[157–162] In addition, other QOL instruments such as the EORTC-HN35 and the FACT-H&N, measure symptoms such as xerostomia, taste changes, pain, fatigue, etc, which are related to head and neck cancer treatment and can have an impact on overall QOL.[163,164]

Instrumental assessment of swallowing should be performed to evaluate swallow physiology. The videofluoroscopic swallow study (VFSS), also known as the MBS assessment, should be conducted to assess oropharyngeal swallow physiology, as well as screen esophageal phase swallow functioning.[165,166] Once the swallowing impairment is defined, therapeutic strategies are implemented during the evaluation to determine whether swallow safety or efficiency can be improved.[165] Flexible endoscopic evaluation of swallowing (FEES) can also be utilized to assess pharyngeal phase swallowing and infer components of oral phase functioning.[167] Therapeutic strategies can also be implemented during the FEES examination to determine whether swallow safety or efficiency can be improved. Alterations in anatomy that result from ablative and reconstructive surgery can be identified with both techniques. Baseline instrumental assessments are recommended pretreatment to define initial swallow functioning.

During the functional assessment, once the speech or voice impairment has been identified, trial therapeutic strategies should be attempted to determine whether the impairment can be modified, such as improving articulatory precision in a dysarthric oral cancer patient, improving voice quality in a dysphonic patient, or improving intelligibility by modifying rate, loudness, or breath support in a patient with reduced intelligibility. In addition, therapeutic exercise strategies can be implemented once

instrumental assessment of swallowing has been conducted to improve oral and pharyngeal phase swallow functioning.[168]

Outcomes

Functional outcomes, including oral outcomes, performance status, and patient-rated QOL, have been examined in patients who have undergone oral tongue resections. Although patients overall demonstrated lower maximal lingual strength than seen in healthy individuals, patients who demonstrated lingual strength above a cutoff of 30 kPa demonstrate better speech and swallow functioning, performance status, and QOL than those with lingual strength <30 kPa.[136] Jaw ROM also correlated with normalcy of diet and performance status.[136] In addition, performance status correlated with patient-rated QOL in these patients. Adjuvant therapy of radiotherapy or chemoradiotherapy resulted in significantly poorer functioning.

Tongue ROM has been found to correlate with performance status, oral outcomes, and patient-rated QOL in the partial glossectomy patient.[139] In 36 patients who underwent ¼ to ½ tongue resection with and without free flap reconstruction, patients overall demonstrated lower tongue ROM scores than seen in healthy individuals. However, these patients scored a mean of 75 on the Performance Status Scale Normalcy of Diet domain,[145] indicating crunchy solid foods, as well as a score of 83, indicating ability to eat in public, despite any diet modification. The Karnofsky Performance Status mean score for these patients was 93, indicating the ability to carry on normal activity. Diet type correlated with tongue ROM, with higher tongue ROM scores correlating with fewer diet restrictions. Patient-rated QOL in these patients revealed overall scores of mildly impaired eating QOL. When examining tongue ROM and QOL, tongue ROM significantly correlated with QOL, with higher tongue ROM values correlating with improved QOL. A similar correlation was found with the Speech Handicap Index QOL scores and tongue ROM, with higher tongue ROM scores correlating with better speech QOL scores. Lingual ROM post surgery clearly plays a role in ability to eat and speak and has an impact on patient-rated QOL. When examining the effects of surgery including microvascular free flap reconstruction for ORN of the mandible on functioning, the majority of patients reported improved QOL after ORN surgery.[169] Further, QOL for speech, swallowing, and overall functioning correlated with oral nutrition and performance

status.[169] ORN surgery did not, however, markedly improve swallowing-related QOL for those individuals with preoperative dysphagia due to chemoradiotherapy. Patients undergoing ORN procedures need to be counseled regarding the potential negative impact of prior dysphagia on swallowing after surgery.

CONCLUSIONS

There have been major advances in the management of cancer of the head and neck over the past two and a half decades. Technology has had a significant impact on head and neck reconstruction, impacting on the safety and reproducibility of microvascular surgery and functional dental rehabilitation. The important steps that have led to the current “state of the art,” namely, identification of reconstructive problems, creative problem solving, and then assessment of functional outcomes, must be followed into the future in order to continue to enhance the QOL of patients who undergo reconstruction following surgery for cancer of the head and neck.

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29 Oral and Maxillofacial Rehabilitation of Patients with Head and Neck Cancer

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INTRODUCTION

Optimal care of patients with cancer of the head and neck requires the combined efforts of a team of health care providers whose collective goal is not only to cure patients of malignant disease but also ensure the well-being and maintain quality of life of patients during and after treatment. In most patients with cancer, challenges seen in the oral cavity mirror those of the general population—moderate to advanced periodontal disease, dental caries, poorly restored dentition, dental and soft tissue pathologies associated with the use of tobacco and alcohol, poor nutritional status, general hygiene neglect, or a combination of these factors.[1,2] Evaluation, treatment, and prevention of any preexisting oral and dental disease are important aspects of the overall treatment outcome for patients with cancer.[1,2] Patients undergoing aggressive anticancer treatment encounter treatable, if not preventable, oral mucosal and dental sequelae that, if left untreated, could produce morbid events.[3] Complications vary with each patient, depending on the individual's oral and dental status, the type and location of malignancy, and the therapeutic approach.[4] Common and frequent treatment-limiting factors, such

as mucositis, infection, and bleeding, can be minimized and, in some cases, eliminated, if evaluated and treated early by an involved, trained oral oncology team. Early dental intervention can also decrease risk factors for oral complications [e.g., osteoradionecrosis (ORN)]. In some cases, ablated structures can be replaced immediately with prostheses that restore function and esthetics thereby maintaining quality of life.

Treating physicians have a medical, ethical, legal, and fiscal responsibility to ensure that patients receiving surgery, radiation therapy, and/or chemotherapy for cancer of the head and neck receive a thorough, systematic oral examination.[1,4] For decades, physicians have placed a major emphasis on the prevention of malignancies through the identification and control of factors, such as tobacco use and alcohol consumption, which are associated with carcinogenic tissue changes.[5–10] Despite a decrease in smoking, however, the incidence of squamous cell carcinoma of the oropharynx continues to increase; this is attributed to infection by human papillomavirus (HPV).[11] HPV-associated cancers are thought to be more responsive to treatment, and therefore, a de-escalation of treatment has been suggested; however, the oncologic efficacy and preservation of function of this type of reduced treatment remain to be shown in prospective clinical trials.[11] Patients with HPV-related disease are generally younger, and given they have more curable disease, the likelihood is that these patients will live longer and thus have a greater cumulative risk of developing long-term complications including treatment-related oral and dental problems.

Therefore, careful coordination between head and neck oncologists of all disciplines must enlist oral health experts for the assessment and delivery of preventive and rehabilitative oral care prior to the initiation of oncologic treatment. Miscommunication or lack of communication between the treating oncologists and oral health experts can contribute to posttreatment complications.[12,13] Oral oncology/maxillofacial prosthodontics is the branch of dentistry specifically concerned with minimizing the oral morbidities associated with cancer therapy and includes the prosthetic rehabilitation of intraoral and extraoral structures that have been affected by disease, injury, surgery, or congenital malformations.[14,15] Patients should be referred to the oral oncologist as early as possible to ensure the appropriate assessment of their oral/dental status, discussion of the prosthetic treatment options of oral/facial defects, and patient education to minimize the oral morbidities

associated with cancer care. The primary head and neck oncologist can then integrate results of this evaluation into the overall treatment plan.

This chapter describes the scope and integration of oral oncology concepts into the treatment of patients with cancer as well as general and specific aspects of oral complications arising from cancer therapy and outlines practical approaches for preventing, recognizing, and treating the oral sequelae associated with chemotherapy and radiation therapy. This chapter also presents current concepts regarding oral and facial prosthetic rehabilitation and oncologic principles associated with the care of patients with cancer of the head and neck.

GENERAL CONSIDERATIONS

An oral/dental consultation before chemotherapy, radiation therapy, or head and neck surgery is extremely important in the oral management of patients with head and neck cancer.[1,16–21]

Oral complications associated with cancer therapy can be classified into several general types—acute (i.e., stomatitis, infection, bleeding, mucositis, and pain) and chronic (i.e., loss of function, ORN, and xerostomia).[22] In most cases, preexisting conditions strongly influence the development or persistence of these complications in the oral cavity. Simple measures, such as good oral hygiene, can often minimize treatment-induced morbidities (i.e., reduce the incidence and severity of mucositis). Complications arise primarily in three anatomic sites—the mucosa, periodontium, and teeth.[4]

Complications arising during cancer therapy may result either from the malignant disease process itself or from treatment (e.g., complications of chemotherapy related to myelosuppression/immunosuppression, or direct cytotoxic effects of chemical agents on oral tissues). For patients receiving a tumor-ablative procedure involving the oral cavity or oropharynx, the treating oral oncologist should aim to control oral and dental complications. As part of the immediate surgical planning, the oral cavity should be prepared for appropriate prosthetic rehabilitation to correct postsurgical defects. If radiation therapy or chemotherapy or both are planned, the treating physician should be aware that the possibilities of oral complications may be increased; furthermore, the degree and type of oral sequelae may affect the patient's compliance with or continuation of cancer treatment.[23–26] Radiation therapy

may directly damage oral mucosa, salivary glands, bone, and oral musculature, resulting in xerostomia, infection, ORN, trismus, dermatitis, extensive dental caries, abnormal bone development and healing, and alteration in taste acuity.[1,17,27,28] Preexisting oral disease may increase the risk and severity of oral complications.[17,25,29,30]

An evaluation of the head and neck, an oral/dental clinical examination, and an intraoral radiographic evaluation should all be performed during the initial visit. Selected dental radiographs are essential in evaluating potential areas of infection that are not obvious on clinical examination (e.g., periapical tooth disease, interproximal caries, residual cysts, and impacted or partially erupted teeth). In addition, the oral oncologist should gather and record the patient's history of present illness, past medical and dental history, social history, review of systems, current medications, and adverse drug reactions, as well as the anticipated cancer treatment plan. From this information, the oral oncologist can plan treatment to meet oral needs in the context of the patient's overall status; however, treatment of malignancy must always take priority over reduction of potential complications.[1,31] Complicated, laborious, and costly prosthetic restoration of teeth should be avoided until after cancer therapy is completed. The overall oral/dental goal is to remove not only current foci of infection but also potential foci of infection as this may increase the risk of ORN and other oral challenges (i.e., teeth that are nonfunctional, noncleansable, and nonrestorable).

The oral oncologist should communicate with the treating physicians to be aware of the diagnosis and staging malignancy, the goals of proposed therapy, the patient's prognosis, the type and dose of therapy to be administered, and the timing of treatment. If radiation therapy is to be used in the head and neck area, the oral oncologist must know the volume of tissue to be radiated, the treatment schedule, the dosimetries, the fractionation scheme, the method of administration (e.g., external beam radiation therapy or brachytherapy), the type of energy (e.g., proton, photon, or electron), and the total dose to be administered.[16,18,32–36]

Oral oncologists should educate patients using tobacco, alcohol, or illicit drugs as to the harmful physical effects of these agents and explain their possible impact on oral health as well as the malignant disease process.[37,38] In addition, the treatment team should immediately discourage further use of these substances and should provide information about and referrals to

cessation programs. The nutritional status of patients should be assessed, and counseling should be provided, if needed, to enable patients to avoid debilitation, which may result in delayed wound healing and increased susceptibility to dental caries.[27,28,39–41]

The oral oncologist's initial examination and early treatment of the patient are directed at documenting and managing any preexisting acute or chronic pathologic conditions, such as dental abscesses, advanced periodontal disease, dental calculus causing gingivitis, partially erupted teeth with the potential for pericoronitis, or soft tissue trauma, which may be factors in the treating physician's selection of an overall cancer treatment strategy.[1,22] Even if the planned cancer treatment is not toxic to the mucosa and is not myelosuppressive, the potential for oral complications remains. Additionally, the cancer may eventually progress, requiring prompt and aggressive therapy; for that reason, the patient's oral and dental status should be optimized to ensure minimal predictable complications. The periodontal status and degree of tooth decay are evaluated, as are the patient's ability and initiative to maintain optimal oral hygiene.[42] Patients must modify their oral care and hygiene techniques to minimize mucosal, gingival, and dental complications that are associated with their specific treatment.[42–44]

One major objective of oral hygiene is to reduce and minimize the formation of plaque—a proteinaceous, adherent, bacteria-laden material on teeth or dental prostheses. Plaque is colonized by normal flora, which is then followed by opportunistic pathogenic organisms. Its accumulation can lead to several harmful conditions, including gingivitis (inflammation of the gingiva), which can progress to periodontal disease (the pathologic loss of supporting bone).[4] Caries is another adverse condition resulting from increased caries-forming organisms and is in itself an important consideration in patients with drug- or radiation-induced xerostomia. Gross caries can result in pulpal involvement and subsequent periapical abscess formation and thus increase the risk of ORN.[4,42,45]

Oral surgery, definitive or intermediate direct restorations, and oral prophylactic procedures may be performed quickly and safely, if needed, under local dental anesthesia, intravenous sedation, or general anesthesia, to expeditiously remove acutely and chronically infected tissues. The oral oncologist must review the patient's medical and hematologic status with the

treating oncologist before initiating any such oral/dental treatment.[46] Prophylactic periodontal procedures and scaling/root planing may be necessary before or during cancer treatment to reduce the oral contamination. Oral hygiene instructions for plaque removal should be emphasized and encouraged, including brushing twice daily with fluoride toothpaste and flossing at least once a day. Oral hygiene procedures may require modification during cancer therapy—for instance, using an extra soft–bristled toothbrush and daily use of topically applied fluoride (e.g., 0.4% stannous fluoride, 1.1% sodium fluoride, or 5,000 ppm sodium fluoride). Customized carriers for fluoride application should be constructed for patients undergoing head and neck radiation therapy and should be used throughout the remainder of the patient's life following radiation therapy.[1,46] Sodium bicarbonate or chlorhexidine gluconate mouth rinses may be beneficial to the patient in reducing microbial and fungal contamination.[47] The prescribed mouth rinse should be carefully selected because some ingredients, such as alcohol and phenol, can be irritating to oral mucosal tissues.

Oral treatment plans should be designed to correct restoration with overhangs, rough or sharp edges on teeth, and any other defects likely to cause soft tissue irritation.[1,48] Patients should be instructed to avoid abrasive foods likely to traumatize soft tissues. Ill-fitting intraoral prostheses should be adjusted to improve fit or not be worn during cancer therapy. Dental implants should be carefully assessed, and their removal should be considered if osseointegration is poor. The implants should not be removed if the implant is stable or if such surgery cannot be performed within 2 weeks before the initiation of cancer therapy.[49–51]

Any potential source of oral infection should be identified and eliminated. Findings of periapical disease, severe periodontal disease, unrestorable teeth with advanced caries, supererupted teeth, and possibly unopposed dentition should be considered for extraction. Endodontic therapy is a viable alternative for infected dentition, provided that the treatment can be expeditiously performed and not delay initiation of cancer therapy.[21,45] To ensure coverage of exposed bone and adequate wound healing, extractions should be performed 2 to 3 weeks before initiation of radiation therapy.[24,52–55] Dental extractions should be performed as atraumatically as possible, and all sharp areas of bone should be removed. This allows for primary closure, which promotes rapid healing.[21,55] ORN can occur in areas

in which teeth were extracted before radiation therapy.[55–57] Sufficient healing time is critical, particularly before radiation therapy is initiated. In general, invasive periodontal surgical procedures should be avoided due to prolonged healing time for the desired results to be achieved.

Patients receiving myelosuppressive or immunosuppressive drugs can develop posttreatment oral or systemic infections, with virus (e.g., herpes simplex virus [HSV]), fungi (e.g., candidiasis), or Gram-positive or Gram-negative microorganisms believed to have originated in the oral cavity.[58,59] As a result, some oncology centers perform microbiologic cultures to assess HIV antibody titers, fungal activity, and microbes with appropriate sensitivity testing as part of the protocol for all oral-related toxicity from cancer therapy. In cases of a positive titer, use of an antiviral agent such as acyclovir, an antifungal agent such as nystatin, or an antimicrobial agent such as clindamycin is common.[60–62]

The following sections describe methods of integrating dental and oral treatment into specific oncologic therapies.

ORAL AND DENTAL ANATOMY

Head and neck surgeons and radiation oncologists should have a thorough knowledge of the oral and dental anatomy to enable accurate communication with the oral oncologist who is responsible for the patient's oral care. It is important to know which teeth will be removed as part of the surgical procedure so the oral oncologist can plan and fabricate an immediate prosthesis. The universal numbering system of teeth is most often used for this purpose. In this system, teeth are sequentially numbered in the adult from 1 to 32, starting with the right maxillary third molar (No. 1), going to the left maxillary third molar (No. 16), then continuing with the opposing left mandibular third molar (No. 17), and ending with the right mandibular third molar (No. 32) (**Fig. 29.1**).[63]

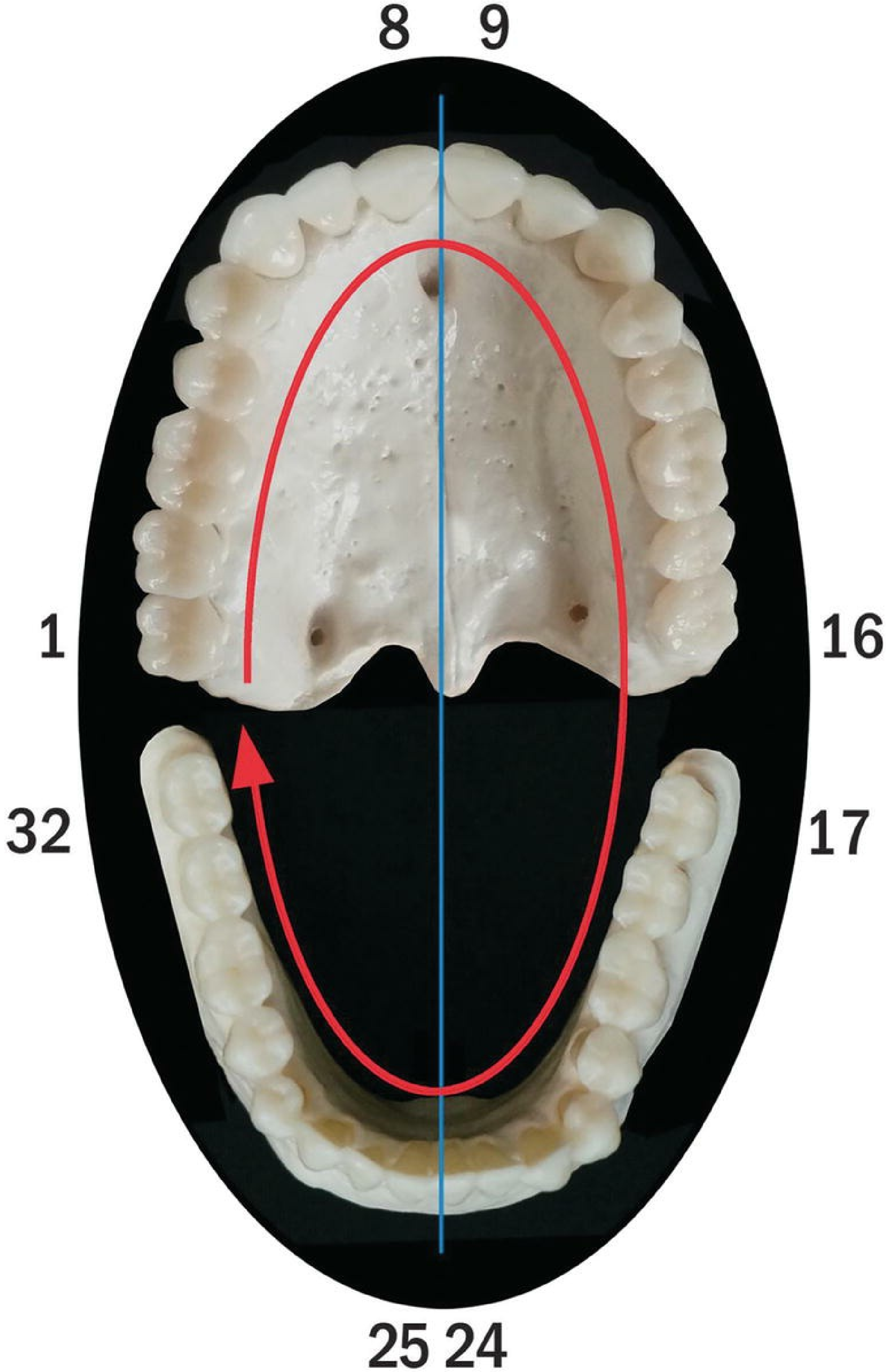
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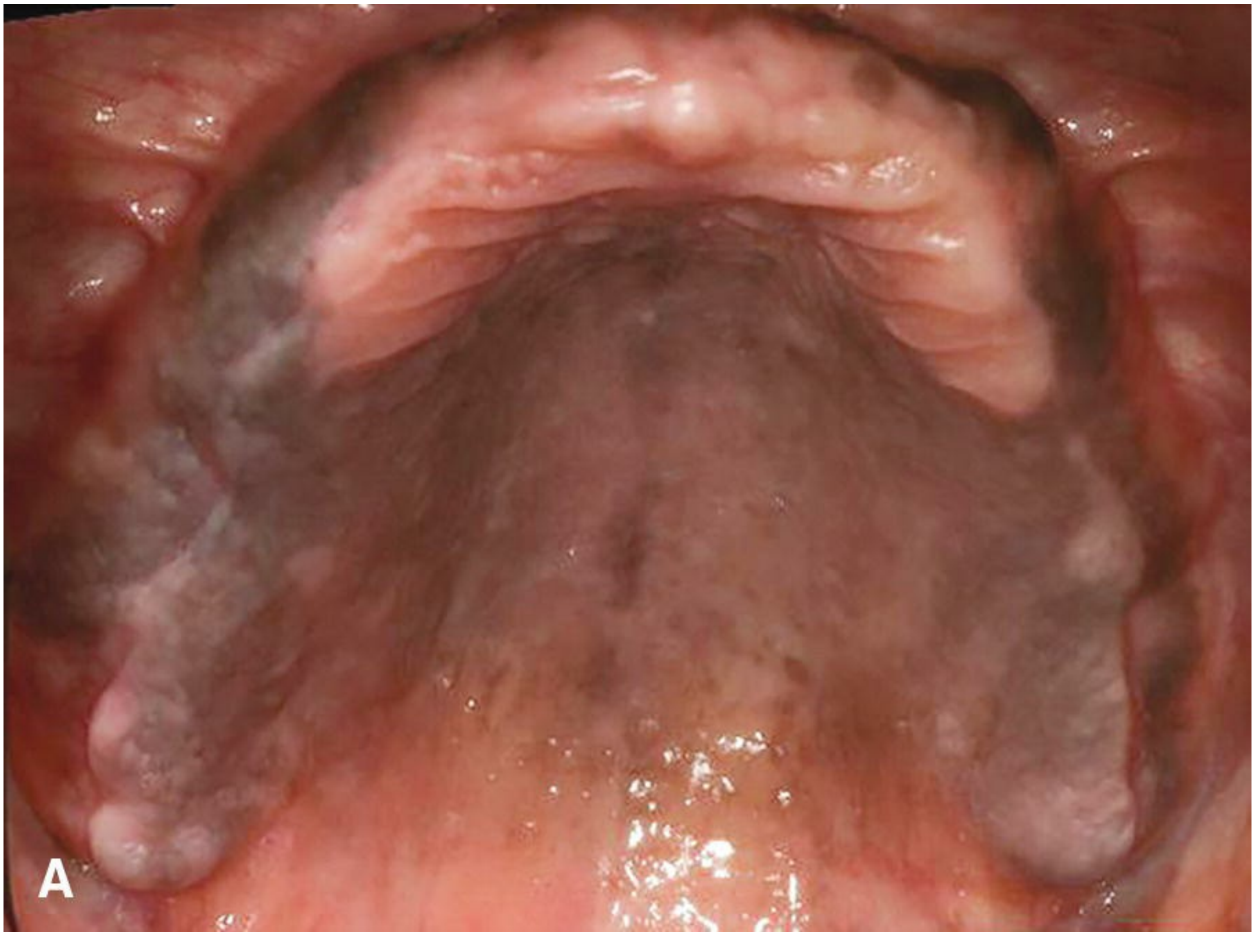
Figure 29.1. The universal numbering system is the accepted method of tooth identification.

Anatomic landmarks important in prosthetic rehabilitation in the edentulous maxillary and mandibular arches are shown in **Figure 29.2**. The stress-bearing surfaces of the edentulous maxilla for a maxillary prosthesis are the tuberosity, rugae, and palatal vault. A maxillary prosthesis is generally retained with suction; if these anatomic regions are not covered appropriately or missing, it is difficult to retain a prosthesis. The mandibular landmarks of importance are the alveolar ridge, retromolar pad, and buccal shelf. The buccal shelf is the primary stress-bearing area for a mandibular complete denture prosthesis. It is important to cover the retromolar trigone to prevent excess resorption of the mandible. Preserving, enhancing, or reconstructing these tissues is important for support and retention of a prosthesis. Teeth that are in good periodontal condition are, of course, essential for the retention and support of the prosthesis. Conservation of the supporting tissues, irrespective of disease removal, should be a priority.[64]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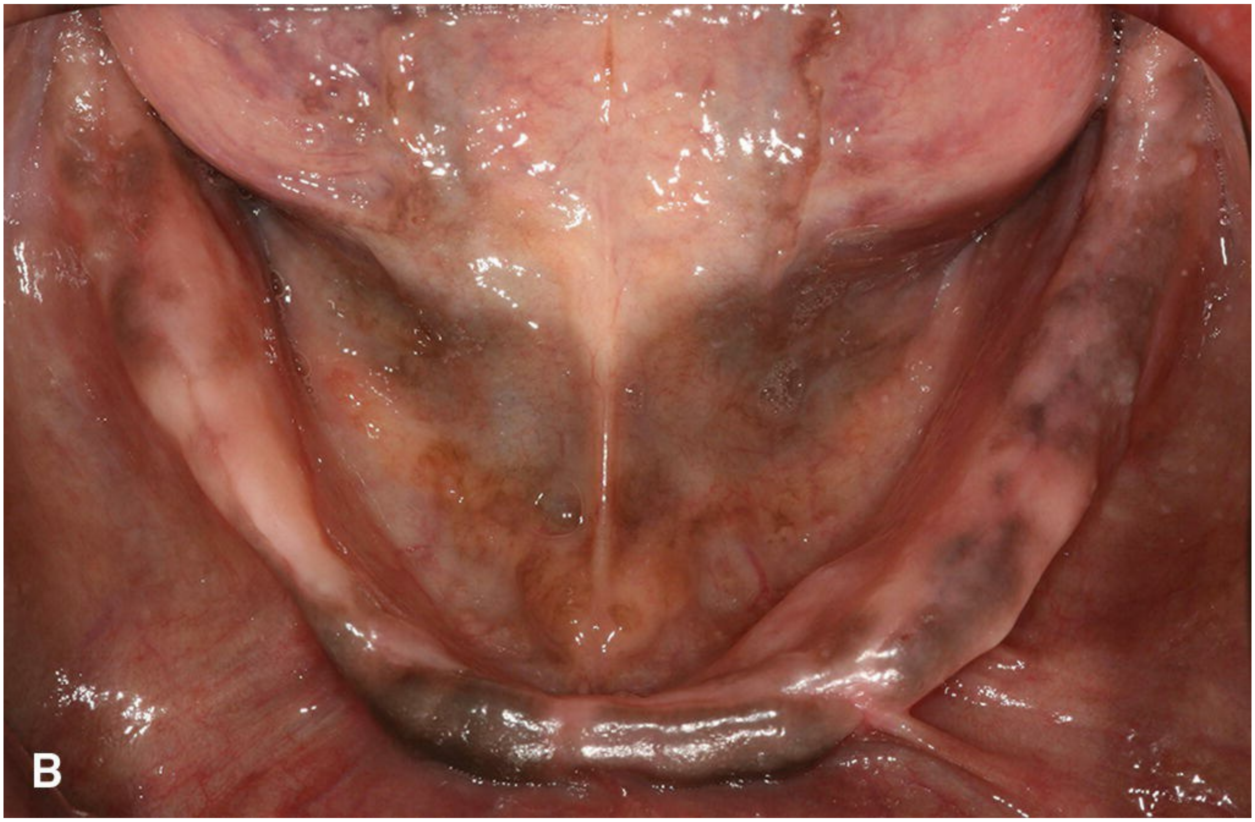


Figure 29.2. Areas that may support prostheses should be conserved, consistent with disease removal. **A:** In the maxilla, these areas include the tuberosity, palatal vault, and rugae. **B:** In the mandible, the areas are the retromolar pad, alveolar ridge, and buccal shelf.

ORAL AND DENTAL EVALUATION

Oral and dental evaluation by the head and neck oncologist should be included in the routine examination of the head and neck. The surgeon should be able to recognize acute or chronic pathologic conditions related to the dentition or supporting structures, such as advanced periodontal disease, gross dental caries, tissue irritation from poorly fitting prostheses, and poor oral hygiene[1] (**Fig. 29.3**). Oral and dental disease should be noted by the oncologist and referred to the oral health provider for evaluation and appropriate treatment.[31]

Figure 29.3. Gross caries, plaque, and calculus formation indicate poor oral hygiene and should be noted in the primary medical evaluation. Mobile teeth indicate bone loss and periodontal disease.

The initial oral–dental examination by the dentist will confirm any preexisting acute and chronic oral pathologic conditions (e.g., dental abscesses, teeth with advanced periodontal disease, or dental calculus causing gingivitis).[1] The dental clinician should obtain appropriate diagnostic radiographs. The most common diagnostic radiographs used in an oral–dental examination are panoramic, periapical, and bite wing radiographs. A panoramic radiograph gives an overall topographic picture of the dentition, maxilla, mandible, sinuses, nasal cavity, and temporomandibular joints.[65,66] These radiographs may be of diagnostic value to the treating oncologist (i.e., diagnosis of bony invasion of the maxilla or mandible by tumor) and are easily obtained in most dental offices (**Fig. 29.4**). Cone-beam computed tomography (CBCT) has become an invaluable tool not only in diagnosis of oral pathology but also in three-dimensional planning for endosteal implants (**Fig. 29.5**).

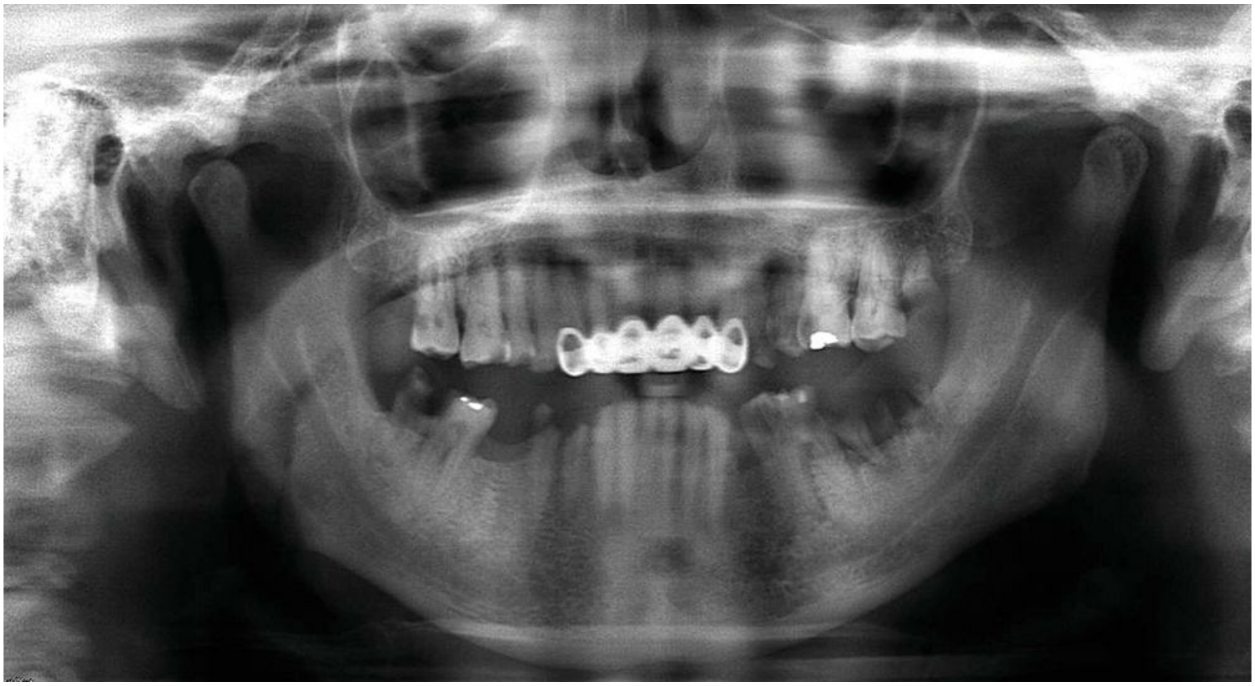
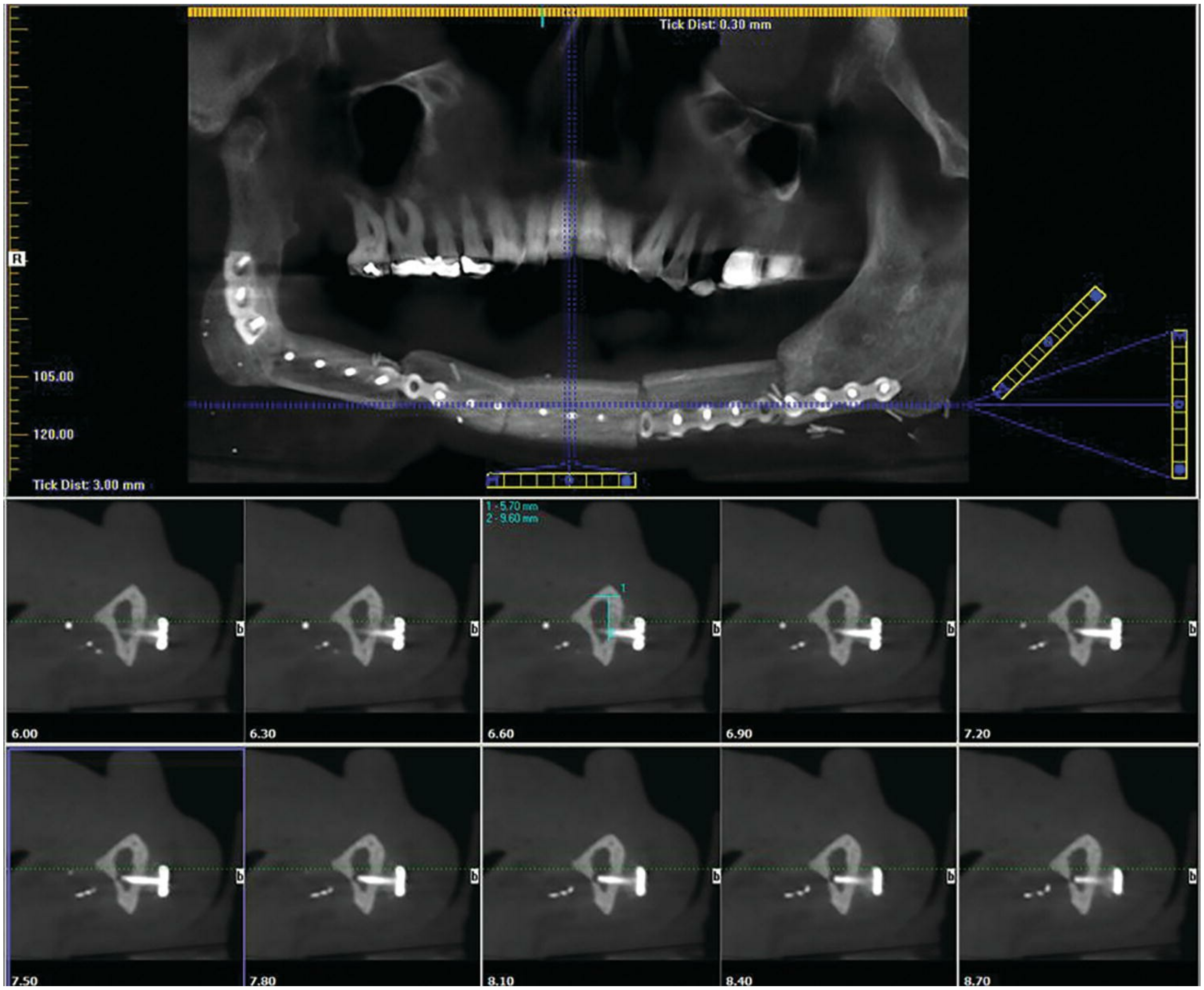


Figure 29.4. A panoramic radiograph is a valuable diagnostic aid that gives an overall impression of the dentition, maxillas, mandible, sinuses, and related structures. Note the broken teeth, rampant caries, and periapical abscesses in this patient, who has received head and neck radiation therapy and has developed multiple oral complications.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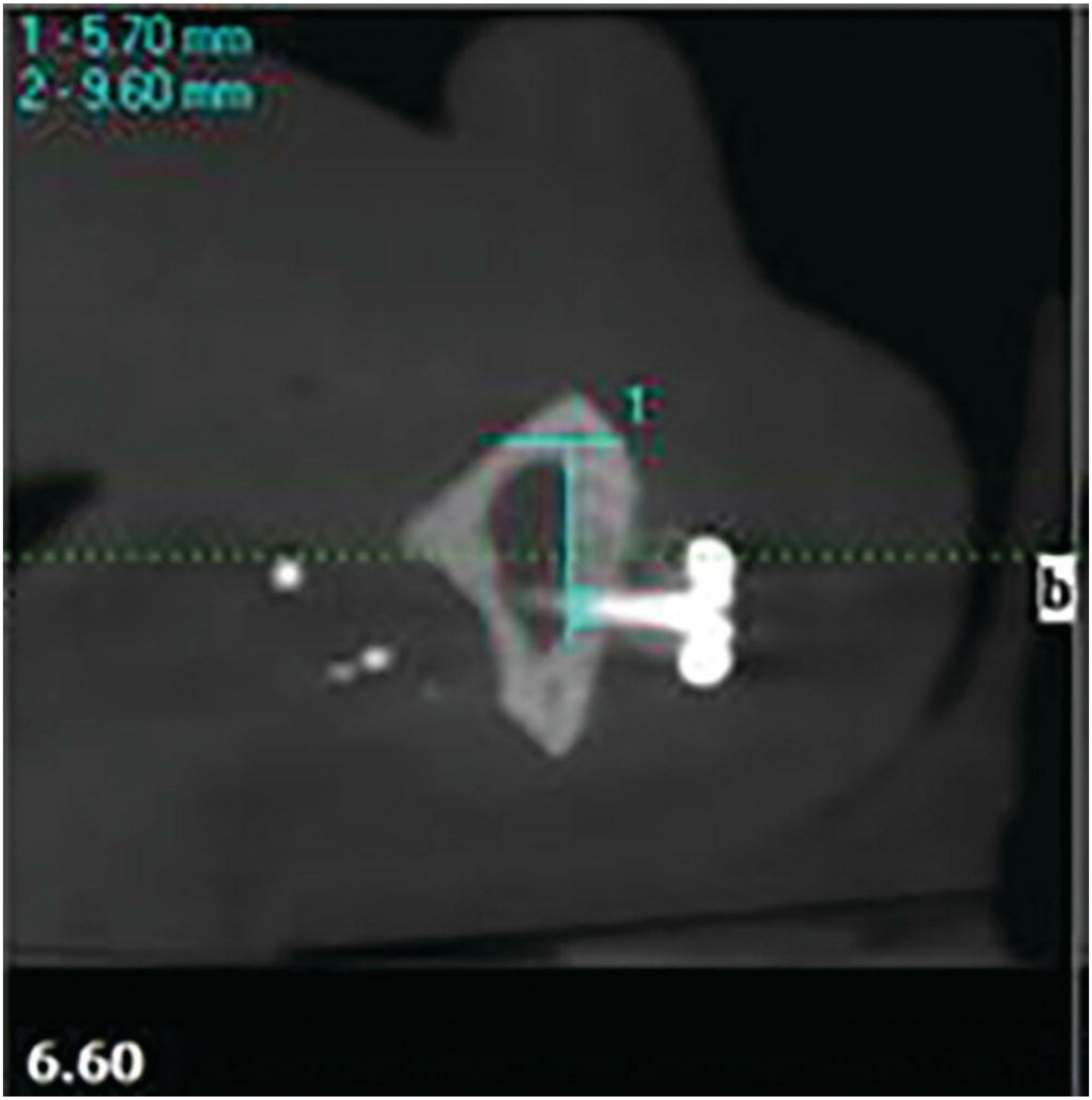
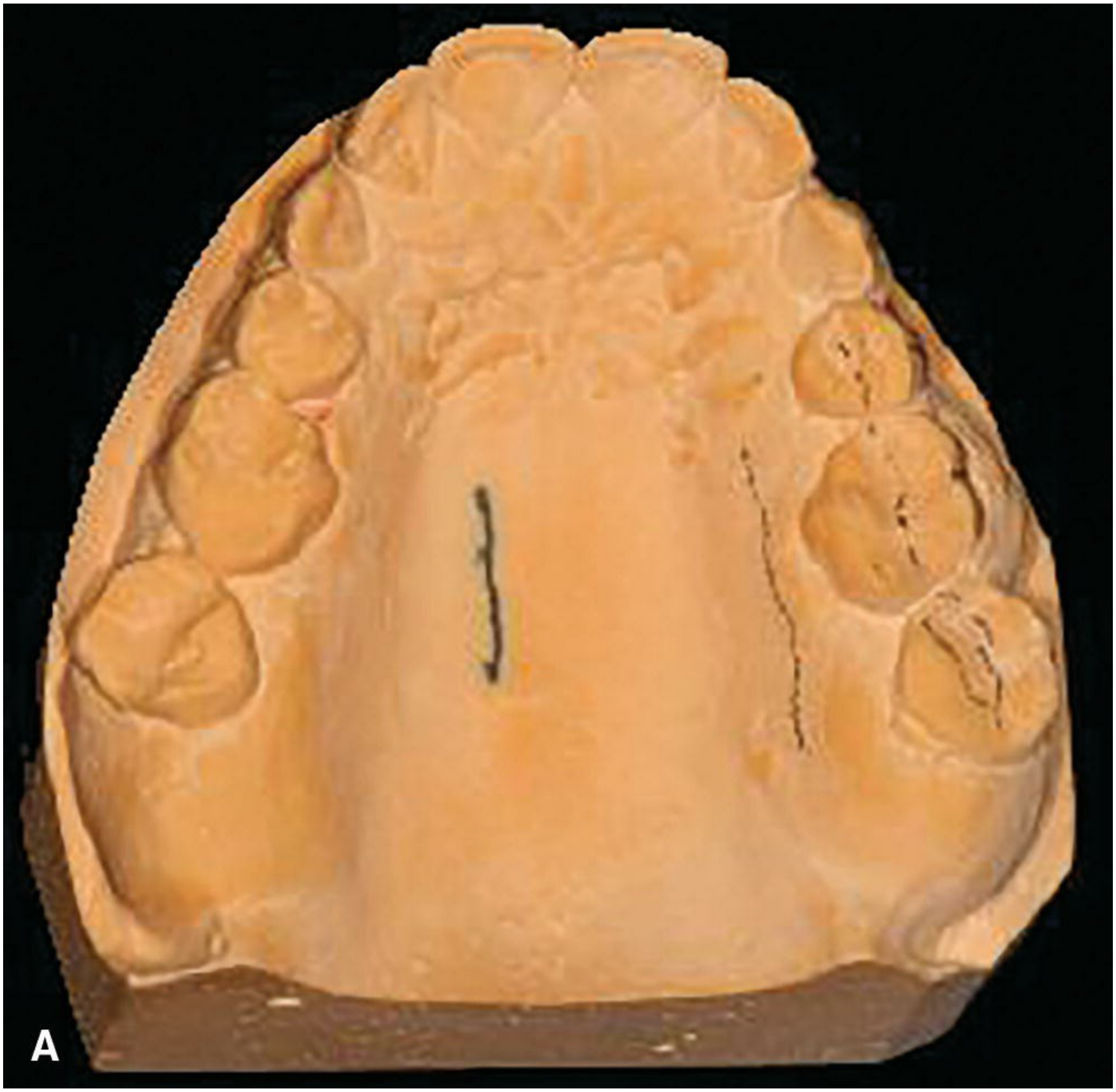


Figure 29.5. This defect has been reconstructed with an osteocutaneous fibula graft. A cone-beam CT was made in order to aid the planning of endosteal implants. In order to use this implant site, the mandibular reconstruction screw must be removed. (Note the measurements made in blue.)

The dentition is evaluated with respect to its periodontal, restorative, and hygiene status. The oral oncologist should also determine the ability of the patient to maintain oral hygiene after the cancer treatment. Every effort should be made to eradicate any areas of infection before treatment

associated with the dentition. Nonrestorable teeth can be removed at the time of the ablative surgery. Teeth should not be removed indiscriminately because of their potential to support and retain a prosthesis. Impressions of the maxilla, mandible, or external facial structures are made at the time of initial evaluation; the casts obtained from these impressions may be helpful in fabricating surgical prostheses, if needed (e.g., a surgical obturator for a patient who has undergone a maxillectomy) (**Fig. 29.6**). Patients are instructed on oral hygiene methods and how oral physical therapy will play an important role in the postoperative rehabilitation period. Pertinent findings associated with the oral and dental examination are then presented at the multidisciplinary treatment planning session.[67,68]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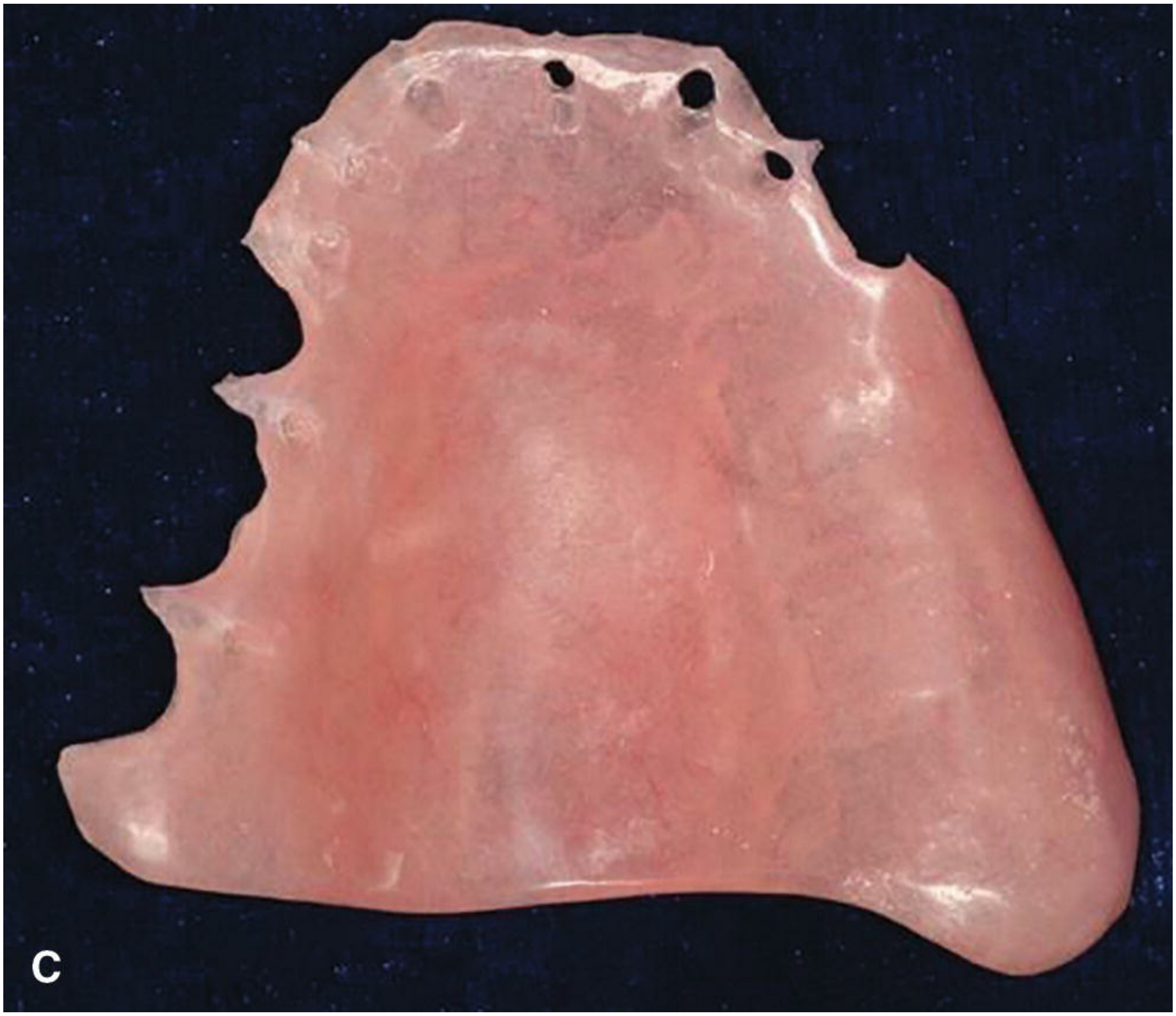


Figure 29.6. A: The cast obtained during the initial dental examination can be used to fabricate the surgical prosthesis. **B and C:** Cast surgery is performed, and an acrylic plate (surgical obturator) is fabricated to be retained with ligature wires, note holes on cameo surface.

Extraction of Troublesome Teeth

The following guidelines are used to identify potentially troublesome teeth for extraction prior to initiating radiation therapy to minimize the risk of ORN. Teeth within the volume of tissue to be radiated that demonstrate moderate or severe periodontal disease, advanced caries, or periapical pathologic conditions should be extracted. Also, partially impacted teeth, unopposed teeth, and teeth that would, if not extracted, oppose a segment of a resected jaw or complicate future prosthodontic rehabilitation should be

extracted. In addition, healthy teeth may need to be extracted if the patient is clinically judged to be unable to maintain adequate oral hygiene following radiation therapy. Fully or deep partially impacted third molars should not be extracted due to extended healing time and risk for permanent damage to the inferior alveolar nerve. Radiologic examination, with either a panoramic radiograph or a CBCT, is the most important diagnostic tool in diagnosing periapical infection, impacted teeth, intrabony cysts, or other hard tissue disease.

Patient Education

The evaluation appointment is the ideal time to present the patient with an oral hygiene protocol designed to minimize or prevent complications associated with radiation therapy to the paranasal sinuses, parotid, nasopharynx, oral cavity, oropharyx, and/or neck. Oral hygiene procedures designed to reduce plaque and oral flora must also be instituted. Because the effects of radiation are permanent, the patient must continue a fluoride protocol throughout his/her life.

Patients who receive radiation therapy to the head and neck area involving the major salivary glands experience reduced saliva flow (i.e., salivary hypofunction or xerostomia).[55] This permanent xerostomia results in dramatic increase in the susceptibility to dental caries, and the severity of the morbidity is dependent on the radiation dose, volume of tissue treated, and the age of the patient when treated.[1] Therefore, patients should be placed on a fluoride regimen as numerous studies have shown that fluoride reduces radiation-induced decay of teeth if used in a systematic, predictable manner.[69,70]

Caries is in itself an important consideration in patients with drug- or radiation-induced xerostomia (**Fig. 29.7**).[1,71] Reducing the potential for dental infection while maintaining optimal oral health can significantly decrease the risk of ORN in a patient who receives radiation therapy or a significant cellulitis in a patient who receives aggressive chemotherapy.[69,72,73] The surgeon should understand the importance of this concept and reinforce compliance at subsequent visits.

Figure 29.7. Radiation-induced xerostomia, as demonstrated by thick ropey saliva, can result in rapid onset and progression of rampant dental caries, which ultimately may result in ORN.

Meticulous oral, dental, and prosthetic hygiene is encouraged as soon as possible after head and neck surgery.[71] In general, patients are hesitant about starting oral and dental hygiene postoperatively because of a fear that the surgical site will be disturbed. Routine oral and dental hygiene can be initiated 2 weeks following surgery. In the immediate postoperative period, within a 2-week period, oral care may be limited to oral lavage and rinses.[1,69,71]

Interincisal opening can be challenging postoperatively, especially following a maxillectomy procedure. Postoperative physical therapy is an additional consideration in rehabilitation, and suitable techniques can be discussed and explained to the patient before surgery and reinforced postoperatively. Stretching can maintain the oral opening and allow the patient better access to the surgical defect and to the remaining oral cavity.[71,74,75] Simple opening exercises using wooden tongue blades or the

fingers may be effective in restoring normal opening after surgery (**Fig. 29.8A**). In more complex cases, devices such as the Therabite or Dynasplint can be implemented (Fig. 29.8B).[69,75]

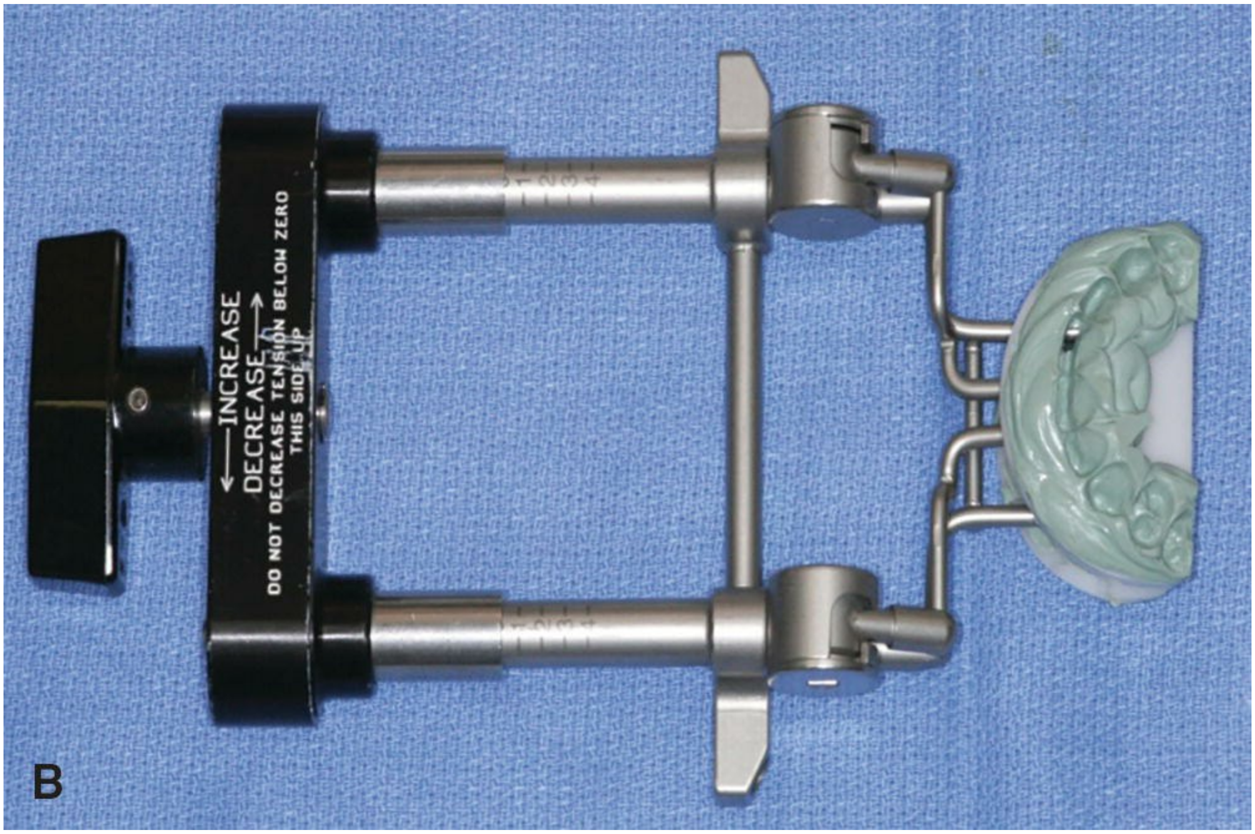


Figure 29.8. A: Physical therapy with active stretching may be helpful for maintaining the oral opening. **B:** A *JDS* device will stretch fibrotic tissues during healing and radiation therapy.

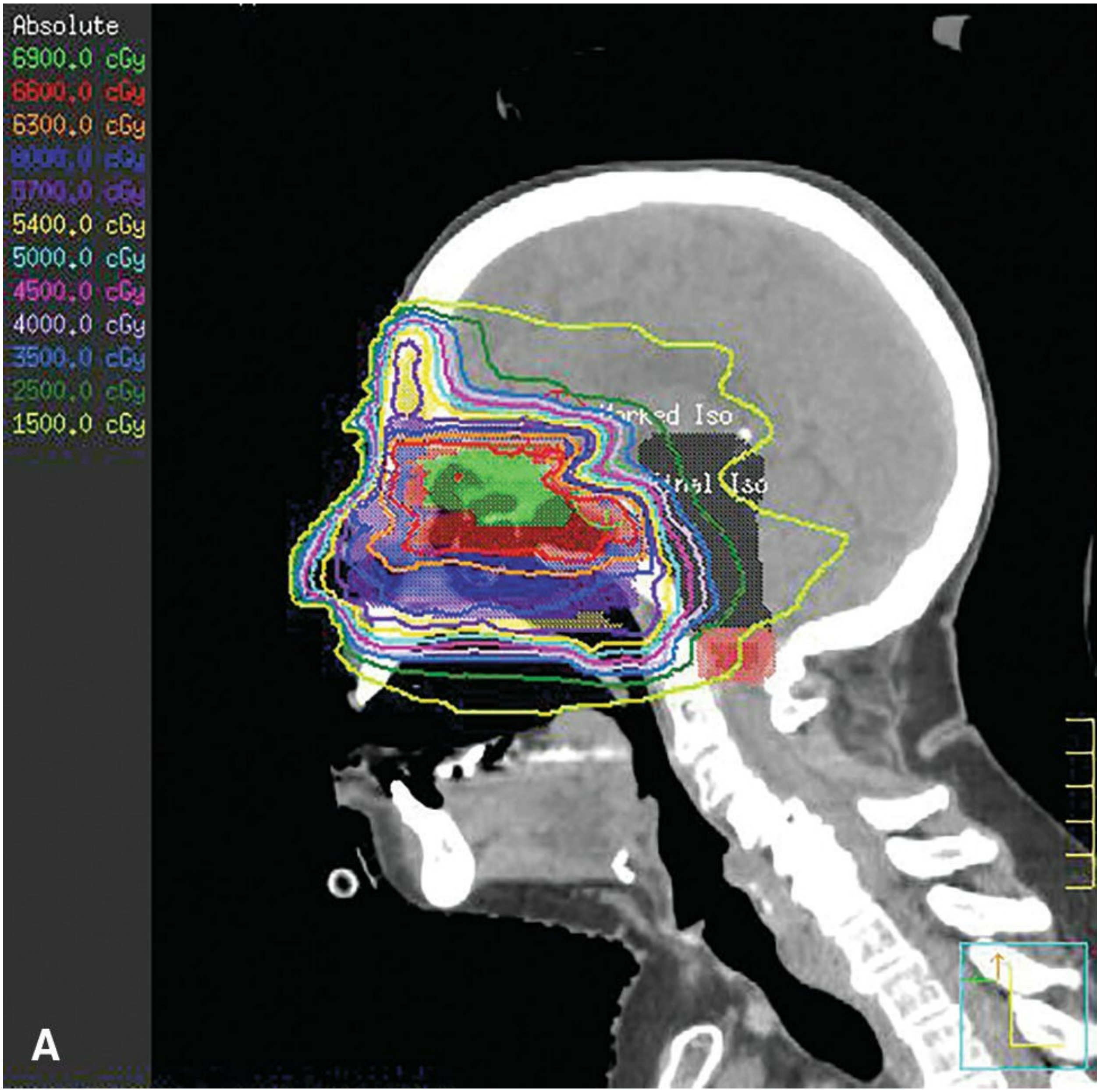
RADIATION THERAPY

More than 80% of patients diagnosed with cancer of the head and neck receive a course of radiation therapy as a component of their treatment.[1,76] Many small or early-stage tumors of the head and neck region can be treated with definitive radiation; more advanced disease often requires a combination of therapies. If surgery is a component of the management strategy for an advanced cancer, radiation may be sequenced so that it is administered either before or after the surgical procedure. Chemotherapy is also used for patients with advanced disease and can be delivered in a neoadjuvant (induction), concurrent, or postoperative adjuvant setting. Studies have revealed that administering chemotherapy concurrently with radiation therapy can improve the therapeutic ratio, resulting in improvement in disease control and survival rates.[9–11,76]

Before a patient receives radiation therapy, the target volume and the surrounding unaffected structures must be defined. The target volume can consist of gross tumor and potential sites of microscopic extension, as well as a volume of tissue to allow for variations in daily patient setup. These volumes are determined by the treating radiation oncologist through physical examination and diagnostic imaging techniques. Treatment planning starts with a simulation—a procedure that is implemented with the use of a special radiographic unit that can reproduce the geometric conditions of a patient on the radiation therapy machine.[36] During simulation, the patient is usually placed in the treatment (i.e., supine) position. Patients are immobilized, usually with a thermoplastic mask, to ensure that the treatment position can be reproduced. Following immobilization, the treatment fields are delineated with the assistance of fluoroscopy and diagnostic radiographs. A CT scan for dosimetry is provided as part of the treatment planning session. The target volume is determined, and normal structures are localized. Treatment portals are designed and verified radiographically. The radiation oncologist prescribes the tumor dose (including fractionation schedules) and, in cooperation with a physicist and a dosimetrist, calculates doses, computes beams, and generates isodose curves.[36] Treatment is implemented by the radiation therapy technician under the supervision of the treating physician and in consultation with the physicist. Periodically, localization films are used and doses on the charts are verified. Tumor response and the patient's tolerance of the radiation treatment are routinely evaluated. The patient is usually evaluated once, weekly by the radiation oncologist.

Radiation Stents

A custom intraoral radiation device, often referred to as a radiation stent, can reduce the radiation dose to unaffected tissue by displacing normal tissue away from the treatment field, minimizing complications and side effects of therapy without compromising total dose to affected area. Patients whose primary tumor is in the oral cavity, oropharynx, paranasal/maxillary sinus, and salivary glands benefit the most by repositioning critical tissue away from the beam of radiation. These radiation stents can be used to depress the mandible and tongue beyond the radiation field, thus minimizing radiation to tissues not at risk or not diseased (e.g., in patients with maxillary sinus cancer, nasopharynx or nasal cancer) (**Fig. 29.9A**).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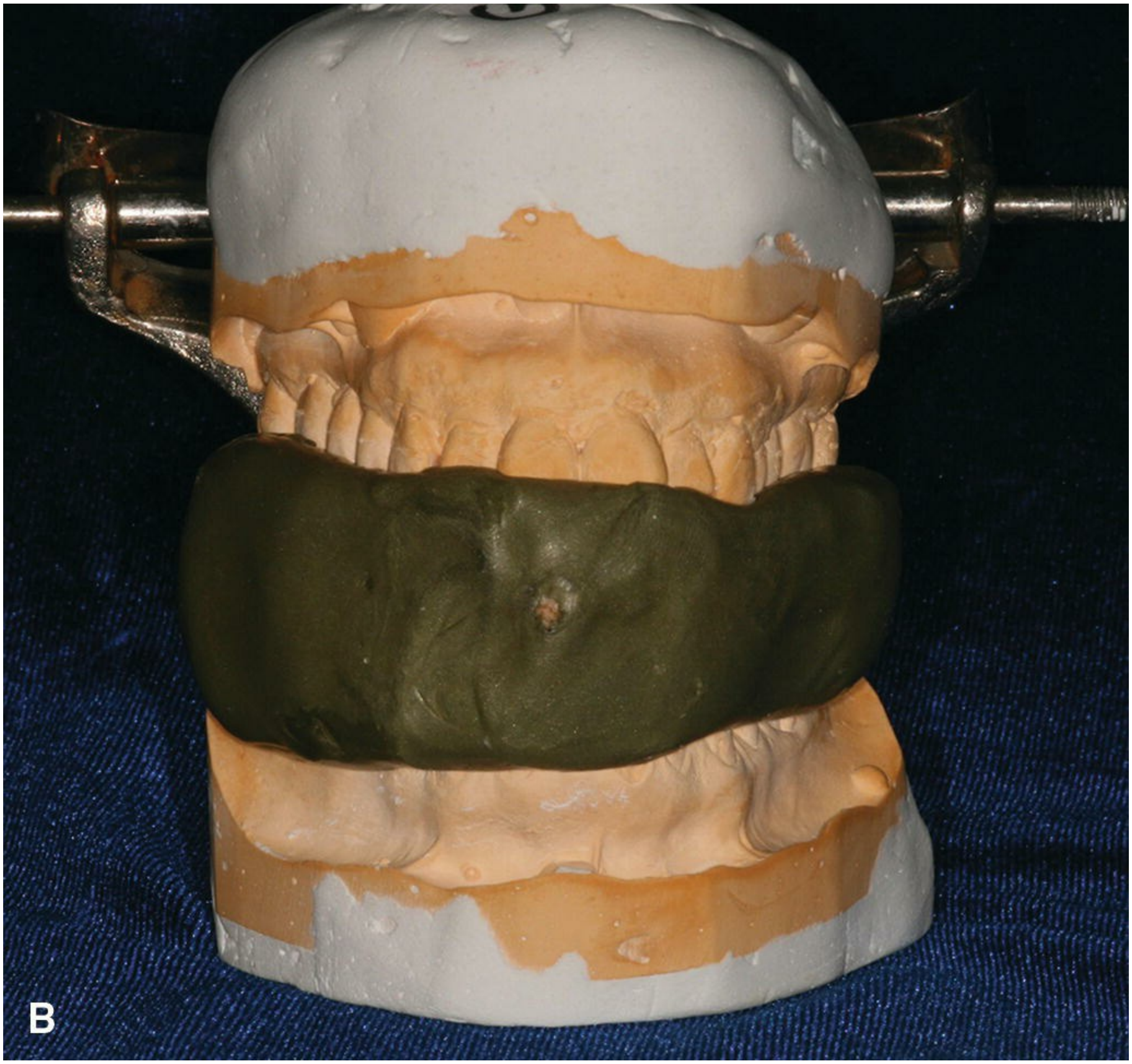
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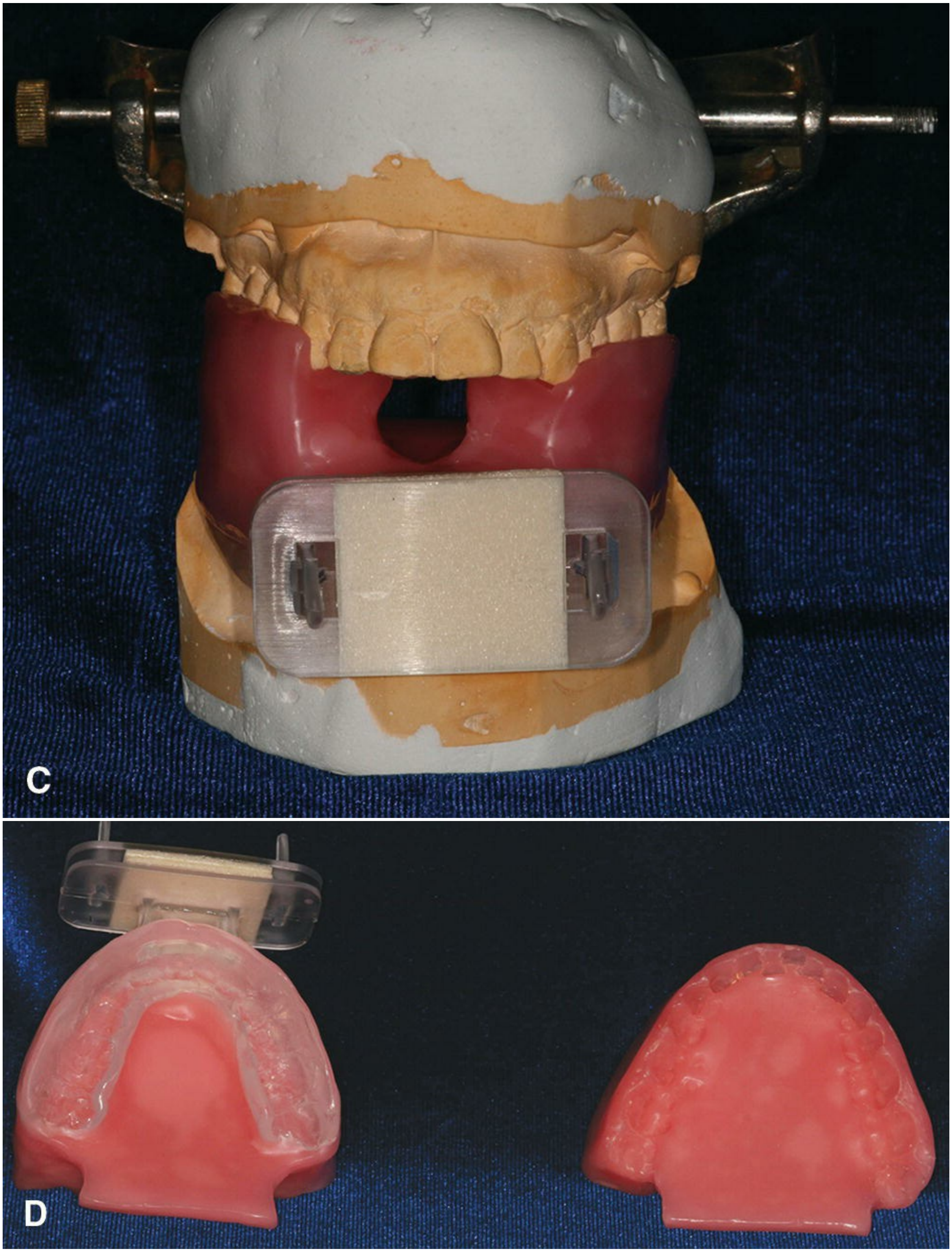

Figure 29.9. A: A CT scan is used for dosimetry purposes in the radiation

treatment planning session. This patient had an olfactory neuroblastoma. Note that the tongue and mandible are completely out of the field of radiation. **B:** Typical records needed for these devices: maxillary and mandibular casts and interocclusal records. **C:** Wax template for final device on mounted casts. **D:** Difference between an IMRT radiation stent and IMPT radiation stent; note the use of the proton bite block. The anteriormost portion of the proton stent is attached to the mask.

These fully customizable devices can be fabricated easily, without complicated prosthodontic techniques. Maxillary and mandibular impressions are required, using a relatively inexpensive material, such as irreversible hydrocolloid. Casts fabricated from these impressions are then placed on a simple hinge articulator with the use of an interocclusal record made at an appropriate mouth-opening distance. The distance is dependent upon the type of device needed, that is, a mouth-opening tongue-depressing stent requires 2 cm opening versus a mouth-opening tongue-deviating radiation stent, which requires 5 mm opening. These devices are also customizable based on the type of radiation to be administered. Proton radiation stents require the addition of a customizable "bite block" (Fig. 29.9B). This bite block attaches to the mask, which allows for a repeatable positioning.

In contrast, the tongue-depressing/mouth-opening radiation device can be fabricated to position the oral tongue and mandible into the field of radiation treatment for repeatable positioning of the oral cavity and tongue during external beam treatment (**Fig. 29.10**).[77] This approach, along with an aquaplast mask, allows for a therapy of exactness and thus eliminates error caused by movement. Such stents are relatively simple to fabricate and are supplied by the oral oncologist.[77,78] If oral oncologic support is not readily available, the radiation therapist or the radiation staff can fabricate a simple device with a tongue blade (composed of Lucite) and a large cork held together with tape, although this measure is not strongly advocated.

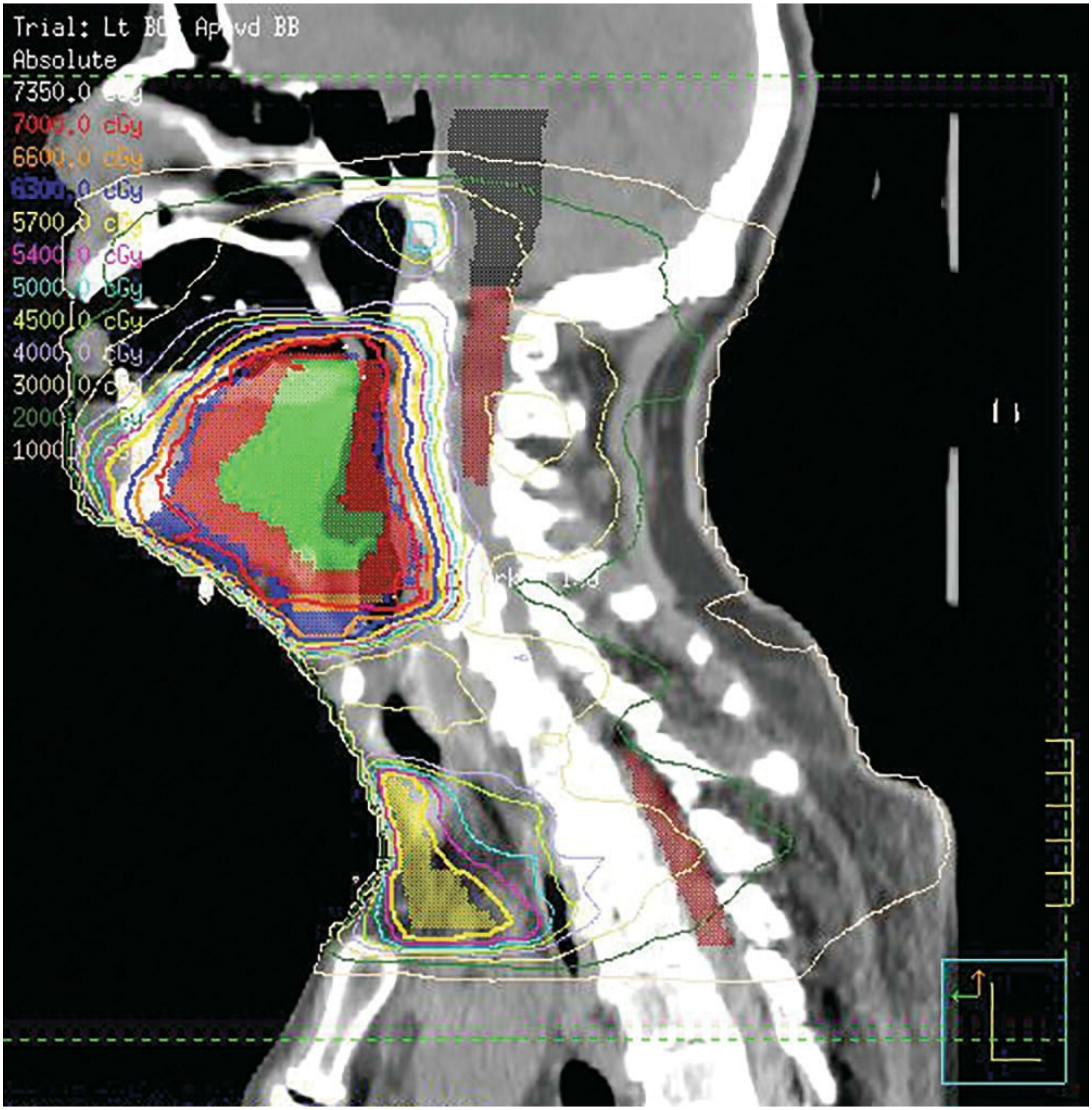
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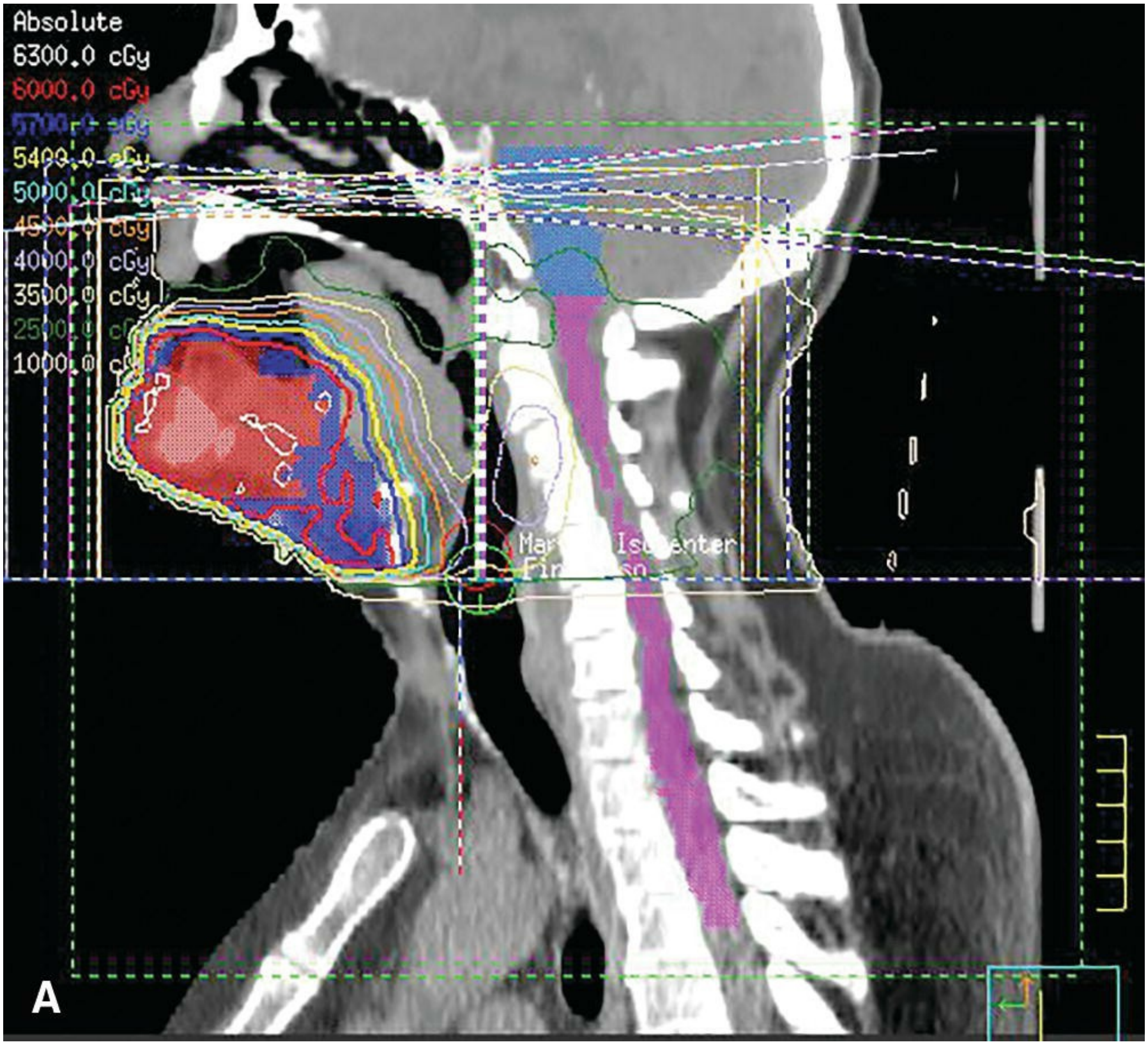
Figure 29.10. The patient has a squamous cell carcinoma of the base of the tongue. The patient has the mouth-opening tongue-depressing radiation stent. Notice that the upper jaw is almost completely out of the field of radiation.

In circumstances requiring radiation of the floor of mouth or anterior oral cavity, the stent design can be modified to protect the oral tongue. Replacing the horizontal tongue blade portion with an inclined ramp and placing the ventral tongue on the ramp permit the tongue to be positioned posterior to the primary treatment field (**Fig. 29.11**).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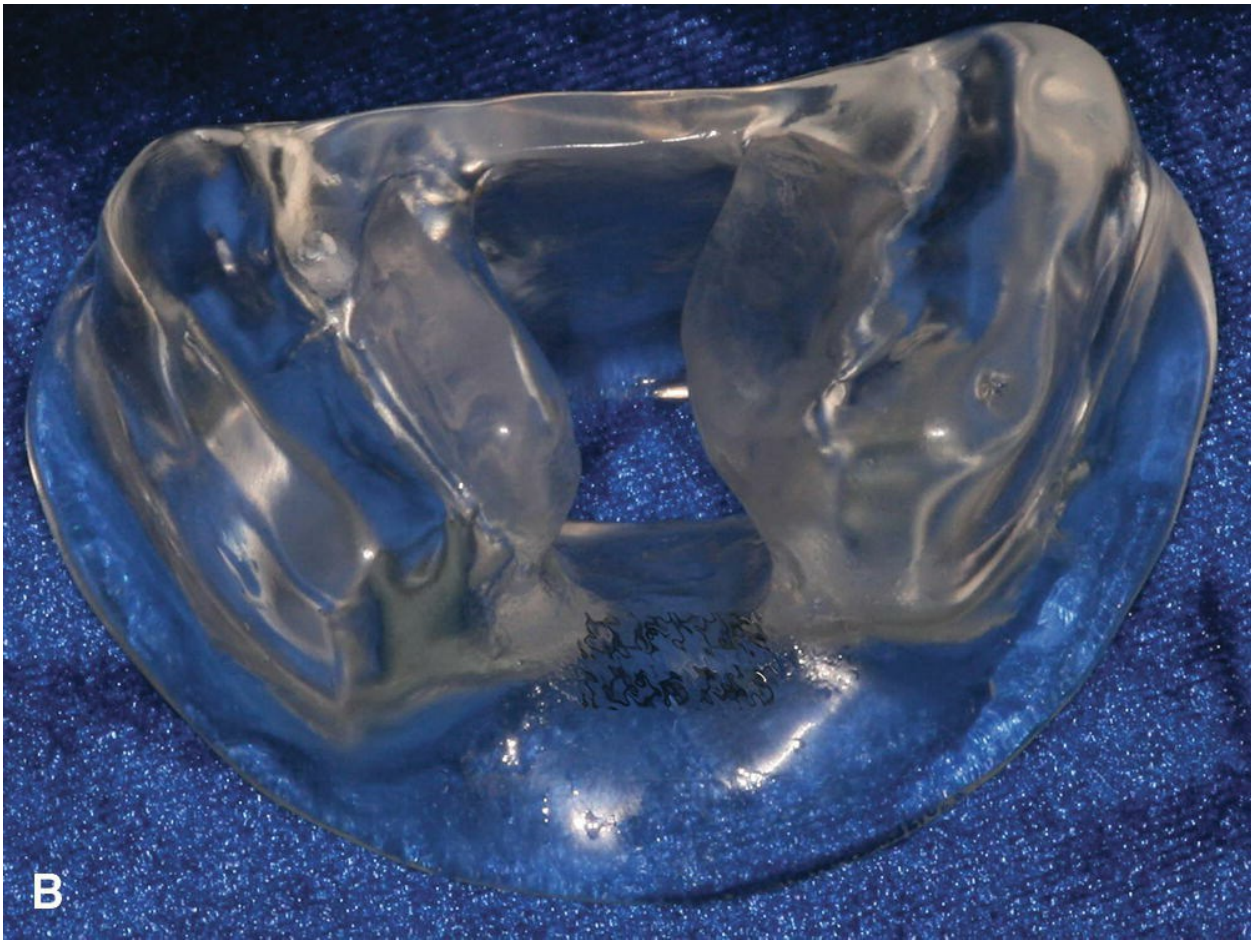


Figure 29.11. A: Patient has a cancer of the floor of mouth; note the reduced dose to the tongue with the radiation stent in place. **B:** The posterior aspect of the stent is designed to displace the tongue posteriorly away from the high-dose radiation.

A further modification of the basic stent design is required if a maxillectomy, a procedure that results in an oroantral communication, has been performed (**Fig. 29.12**). Incorporation of a cradle-like modification into the stent design allows a water-filled latex balloon bolus (Faultless Balloon Rubber Co., Ashland, Ohio) to be supported within the surgical defect, thus eliminating the air gap.[79] This device, along with placement of a tissue-equivalent material in the defect (i.e., saline), permits a more homogeneous energy distribution.

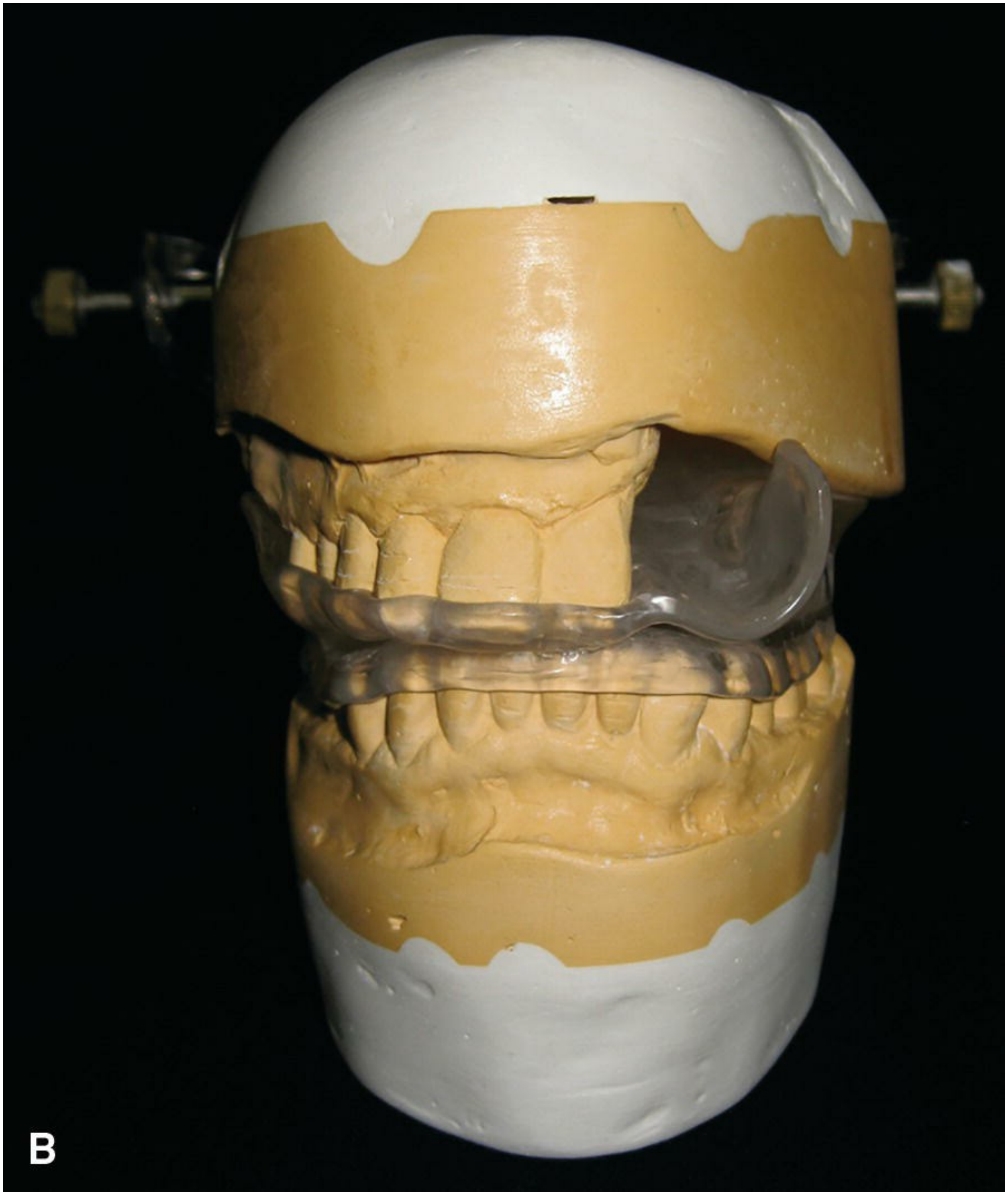


Figure 29.12. A and B: Wax up and final processed balloon-supporting stent. **C:** Lateral aspect of an intraoral stent illustrates the cradle support for the balloon water bolus (tissue equivalent) that is placed into a maxillectomy defect. The balloon is fitted with a No. 12 French catheter to facilitate the injection of water.

Patients who undergo radiation involving a unilateral treatment field benefit from a unilateral radiation device (**Fig. 29.13**). The device, known as a mouth-opening tongue-deviating radiation stent, deviates the tongue and associated tissues to the contralateral side, thus reducing treatment-related morbidity to the contralateral tissues. A Lipowitz alloy is added to the unilateral radiation stent for added protection when the treated tissue volume receives electron beam energy or combined electron/ photon energy weighted 4:1.

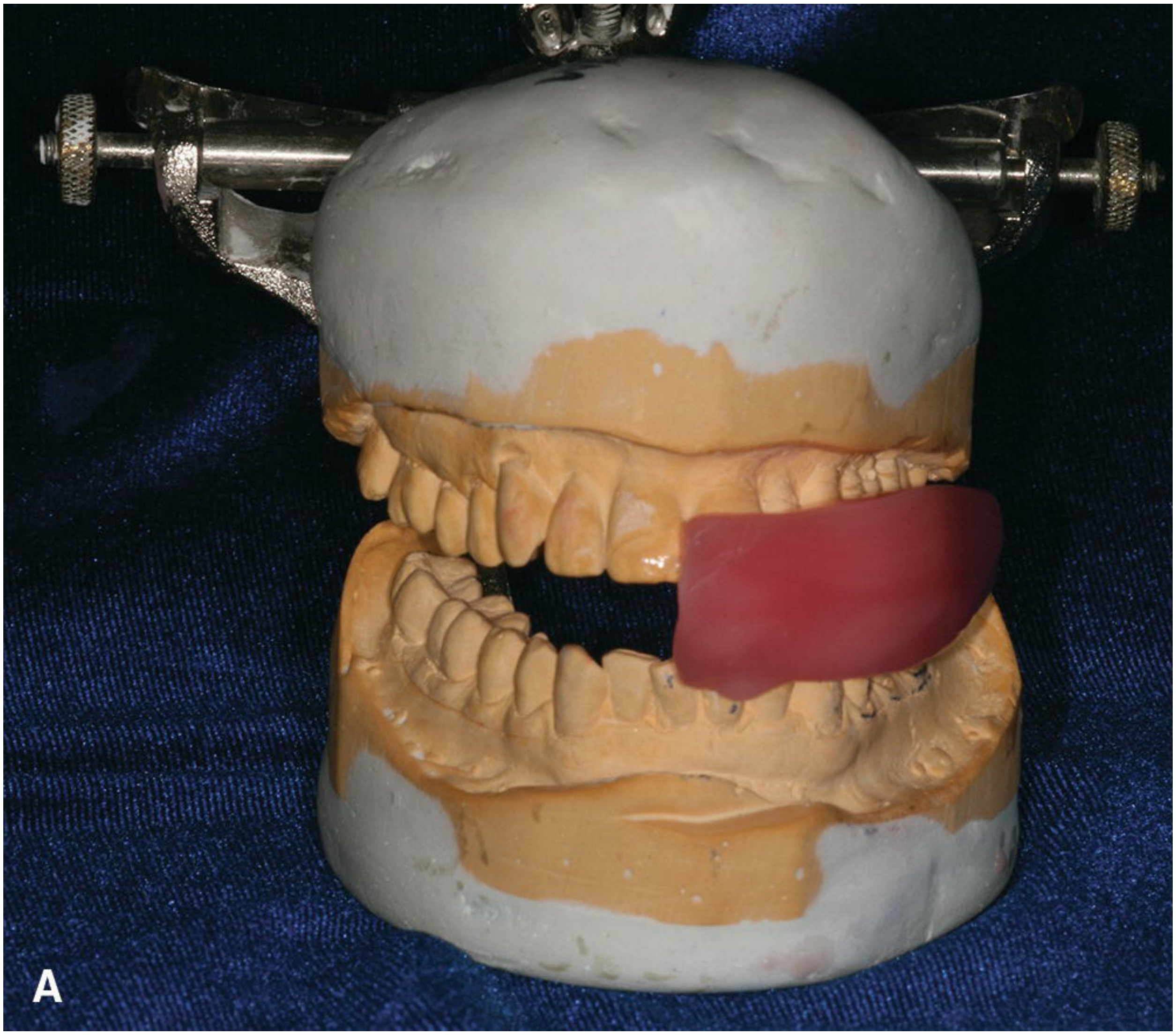

A

Figure 29.13. A: Wax pattern for a tongue-deviating radiation stent. The device moves the tongue to the contralateral side of the oral cavity effectively minimizing the dose to the tongue. **B:** Radiation stent in place. Note that the tongue is deviated to the contralateral side, away from field of radiation.

Oral Complications from Radiation Therapy

Good oral health at the onset of radiation therapy minimizes the risk of complications from therapeutic administration of ionizing radiation to the head and neck. These consequences can be categorized as either acute (e.g., mucositis, infectious stomatitis, alteration of taste or smell acuity, dermatitis, pain, inflammation, and difficulty swallowing) or chronic (e.g., xerostomia, caries, abnormal development, fibrosis, trismus, photosensitivity, ORN, and pain).[1,37,45] The severity of treatment-induced morbidity depends on multiple factors, including radiation dose, energy source, volume of tissue treated, pretreatment performance status, and pretreatment periodontal condition.[55] The radiated tissue is susceptible to dermatitis and mucositis, which are often accompanied by salivary gland hypofunction, dysgeusia, dysphagia, odynophagia, hypovascularity of soft and hard tissues, fibrosis, or

trismus.[1,22,54,55] Widespread oral melanotic hyperpigmentation and hypopigmentation have been reported. Developmental abnormalities of the dentition and jaws may occur in children undergoing head and neck radiation therapy.[80–82] In patients of all ages, altered tissues within the volume of tissue radiated are highly susceptible to infectious processes, with fungal organisms such as *Candida albicans* or other *Candida* species; bacterial infections, including streptococci and staphylococci; and viral infections, especially HSV.[59]

Radiation-Induced Mucositis

Oral mucositis generally occurs 5 to 7 days after initiation of external beam radiation therapy. Oral mucosal changes depend on fractionation, energy source, total dose of radiation, and oral and dental status (**Fig. 29.14**).[55] During conventional daily dosing, the rate of destruction of the basal cell layer in excess of proliferation of new cells creates a net deficit of cells resulting in mucositis. During the course of radiation therapy, the mucosa becomes thin as a result of direct cell death and the sloughing off of epithelial cells.[36,83] Subepithelial edema can evoke an epithelial breakdown. By the end of treatment, diffuse erythema, ulceration, spontaneous bleeding, and white or yellow pseudomembrane formation may be present.[84] Late, radiation-induced changes in the oral mucosa are thought to be due primarily to damage of the microvasculature and the connective tissue stromal elements. Telangiectasia, occlusion of capillaries, thickening of blood vessel walls (lack of tonus), and increased hyaline and collagen deposition contribute to thin, atrophic, and relatively avascular mucous membranes.[76,83] Such changes predispose the patient to hypersensitivity to trauma, infection of the oral mucosa, and delayed wound healing, particularly after minor surgical procedures.[1] Dental hygiene procedures may lead to an increased risk of infection or chronic ulceration during this period.[4,23,37]

Figure 29.14. Radiation-induced mucositis, which has been exacerbated by use of an alcohol-containing mouth rinse.

The grade of oral mucositis can be partially controlled by the elimination of all secondary sources of irritation, such as alcohol, smoking, plaque and calculus, coarse or hot foods, alcohol- or phenol-containing mouth rinses, and sodium products that can further dehydrate oral tissues.[21,84] Many physicians recommend that mouth rinses containing alcohol, phenolics, or astringents be avoided owing to the potential of such agents to dehydrate the mucosa and increase oral discomfort.[1,45,55,82] Treatment of mucositis typically consists of palliative pain reduction therapy; however, the Multinational Association of Supportive Care in Cancer (MASCC), in partnership with the International Society of Oral Oncology (ISOO), completed a review of the relevant literature of treatments for mucositis in 2013, which identified low-level laser

therapy (LLLT) as the most promising treatment.[85–89] A new suggestion was made by this group for LLLT (wavelength approximately 632.8 nm) for the prevention of oral mucositis for patients undergoing definitive radiation therapy without concomitant chemotherapy.[86] However, this strategy has yet to be widely practiced in major centers and remains investigational.

Gingival tissues are sensitive to radiation therapy, and increased gingival recession may occur without signs or symptoms of periodontal inflammation.[23] This recession may be due to the hypovascularity induced by the radiation and to the marked reduction of the quality and quantity of salivary secretions following irradiation.[90,91] There is evidence that a limited amount of gingival revascularization may occur over time, provided that the total radiation dosage delivered was relatively low.[35]

Superinfection

Good oral hygiene is essential to improving oral comfort and reducing the risk of oral contamination. Bacterial, fungal, and viral infections can occur as superinfections with mucositis but are less likely to induce septicemia in patients undergoing radiation therapy than in patients receiving chemotherapy.[1] Patients receiving a concurrent regimen of radiation therapy and chemotherapy may be at greater risk of infectious mucositis than patients treated with either therapy alone, due to increased relative dose intensity and immunosuppression secondary to the myelosuppressive effects of chemotherapy.

With fungal infections, such as oral candidiasis, the pathogens can be invasive, refractory to treatment, and potentially systemically disseminated.[59,82] Candidiasis can manifest as pseudomembranous, hyperplastic, or atrophic (erythematous) oral lesions.[25,59] The sites most frequently affected are the tongue, buccal mucosa, hard or soft palate, and commissura labiorum oris (i.e., angular cheilitis). Diagnosis of candidiasis is based on an exclusion of therapy-related toxicity and a clinical evaluation that includes fungal cultures or visualization of organisms using potassium hydroxide stain or Gram stain.[1,92,93] After the diagnosis has been confirmed, treatment consists of topical antifungal agents such as nystatin oral suspension or clotrimazole troches, depending on the degree of xerostomia.[27,53,59] Patients with unresponsive or disseminated candidiasis

may require systemic therapy, such as with ketoconazole, fluconazole, itraconazole, amphotericin B (liposomal), or a combination of antimicrobials with antifungal therapy ideally under the care of a specialist in infectious disease.[27,59]

At times, infections may manifest in the several weeks following the completion of radiation, during the healing phase (**Fig. 29.15**). These types of lesions typically present as a nonhealing ulcers generally within the field of radiation and can be confused easily with mucositis. Long-standing lesions must be cultured and sensitivity tests completed to establish a causative infective agent. Following identification, the appropriate antibiotic, antifungal, or antiviral should be prescribed.

Figure 29.15. Patient radiated for a carcinoma of the base of the tongue with a nonhealing, painful lesion following radiation therapy. Cultures tested positive for Haemophilus species bacteria.

Osteoradionecrosis

Radiation can permanently destroy cellular elements as well as the vascularity of bone and thus limit the potential for wound maintenance and the ability to heal after infection or trauma (e.g., dental extraction, alveoloplasty).[94,95] Further, the risk of complications following trauma or

oral surgical procedures in an irradiated field can be highly significant, depending on a predetermined threshold of radiation, and can result in ORN (**Fig. 29.16**).[54,55,57,95] For these reasons, elective oral surgical procedures, such as soft tissue surgery, are contraindicated within the radiated field owing to the potential for treatment-induced hypovascularity, hypocellularity, and hypoxia; however, noninvasive dental procedures can safely be performed including oral prophylaxis, radiography, and direct restorative (i.e., fillings), endodontic, and prosthodontic procedures (i.e., crowns and dentures).[1,37,45] Optimal oral health must be maintained during and after radiation therapy; however, to avoid soft tissue injury during the postradiation healing period, patients must curtail all but the most basic oral hygiene procedures (i.e., tooth brushing, flossing, and fluoride therapy). It is important after radiation therapy that dental caries or traumatic injury that could lead to ORN be detected and treated; however, ORN can occur spontaneously.[96,97]

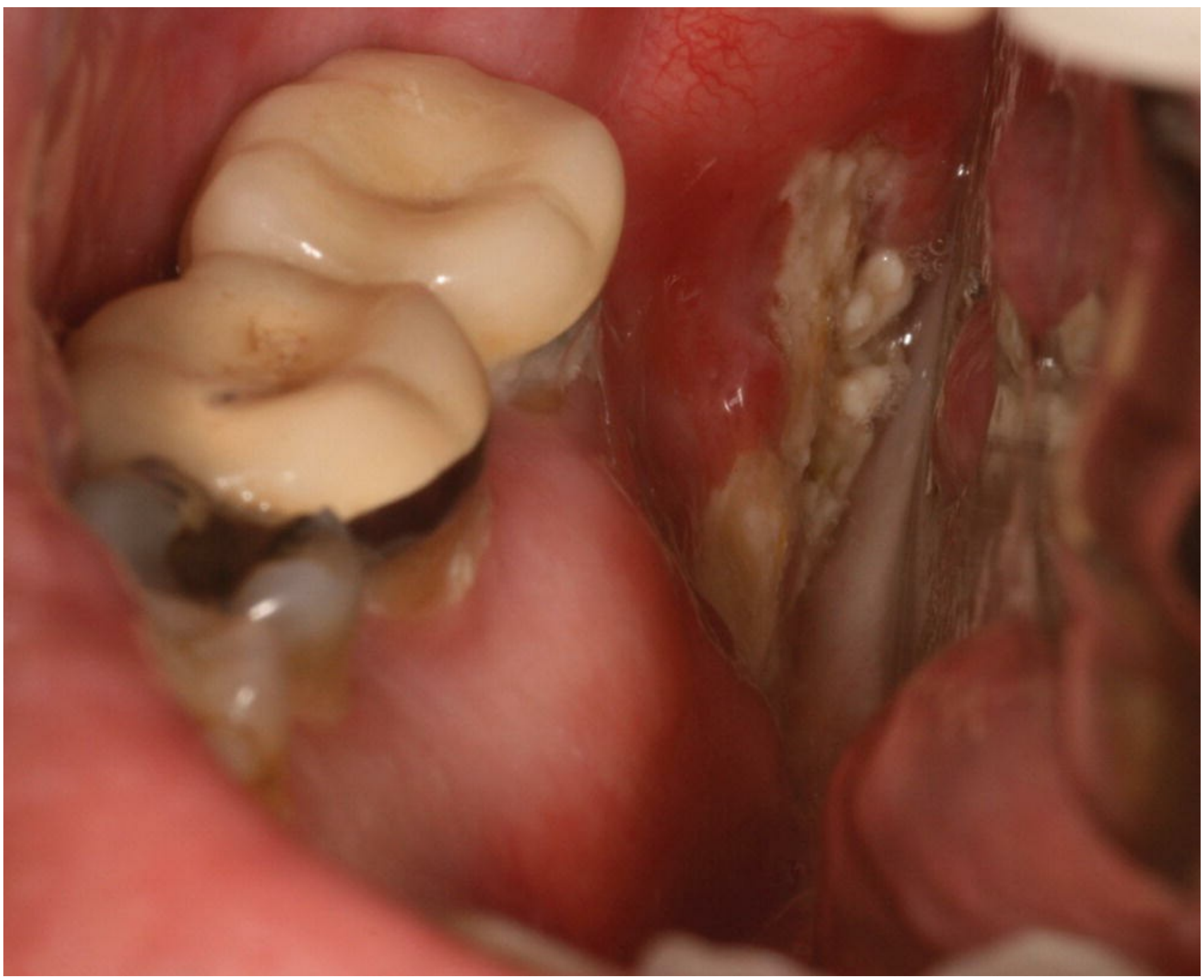


Figure 29.16. ORN following radiation therapy thought to be the result of trauma from intubation.

If oral or periodontal surgical intervention is required after radiation therapy, the clinician should discuss with the treating radiation therapist the volume of tissue radiated and specific treatment parameters and should request a copy of the treatment summary and the dosimetries. Generally, oral surgery, that is, dental extraction or endosseous implant placement, is discouraged in tissue that has received high-dose radiation due to risk of ORN and increased implant failure. Similarly, implants placed into radiated osteocutaneous fibula reconstructions have also shown an increased rate of failure.[98] For teeth that are nonrestorable, conservative measures such as endodontics and crown amputation are preferred over dental extraction. In cases where oral surgery is unavoidable, preoperative hyperbaric oxygen (HBO) therapy administered after radiation therapy is thought to increase the potential for wound healing while reducing the risk of ORN by promoting angiogenesis and osteogenesis, although this remains to be somewhat controversial in the literature.[73,99,100] To date, there are no well-structured, randomized clinical trials to suggest that benefits of HBO therapy. There are contraindications to treatment with HBO, including, but not limited to, pneumothorax and distant metastatic presentation; however, decision to use HBO remains based on empirical judgment and clinician dependent.

HBO therapy can be used as an adjunct to debridement (sequestrectomy) in the treatment of ORN, along with parenteral antibiotics (as dictated by bone culture results).[99,100] Benefits of HBO therapy include improved wound healing in infected ischemic tissue, osteoclastic stimulation, the restoration of normal defense mechanisms responsible for bacterial killing, and the direct killing of anaerobes. Oral oncologists usually prescribe according to the Marx protocol, consisting of 20 preoperative HBO treatments followed by 10 postoperative treatments.[73,101] This prescription may be altered by increasing the number of postoperative HBO treatments to 20 treatments, as decided by the treatment team, to maximize the wound-healing capacity of the patient; however, little benefit was found in patients who received over 40 total treatments. Along with HBO therapy, a specific oral care regimen is indicated to augment wound healing. In such cases, tissues should be managed gently, that is, flapless dental surgery, and antibiotic coverage is required. Local

anesthetics containing epinephrine should be avoided, when possible, to prevent further vascular constriction.[21] Successful placement of endosseous implants in radiated fields with a pretreatment regimen of HBO therapy has been reported; however, there are also reports of initiation of ORN by such elective surgical intervention even when appropriate measures were taken.[96,97]

HBO therapy is time-consuming and expensive and must be performed in an accredited wound care center. When compared with postradiation oral surgical treatment consisting of radical debridement and reconstruction, HBO treatment can be cost-effective if extensive surgery is avoided. HBO may preclude the need for jaw resection and microvascular surgery. In cases in which resection and reconstruction are inevitable, there seems to be minimal benefits from preoperative HBO.

Dental Caries

Dental caries is a common postradiation morbid sequela that is often exacerbated by xerostomia (see **Fig. 29.17A and B**). Radiation of major salivary glands leads to qualitative and quantitative changes in salivary secretions,[1,102,103] thus increasing plaque and mucoid debris accumulation and reducing the salivary pH as a result of a decreased buffering capacity of saliva.[91] These conditions create a cariogenic oral environment, particularly in patients ingesting a diet high in carbohydrates or sucrose.

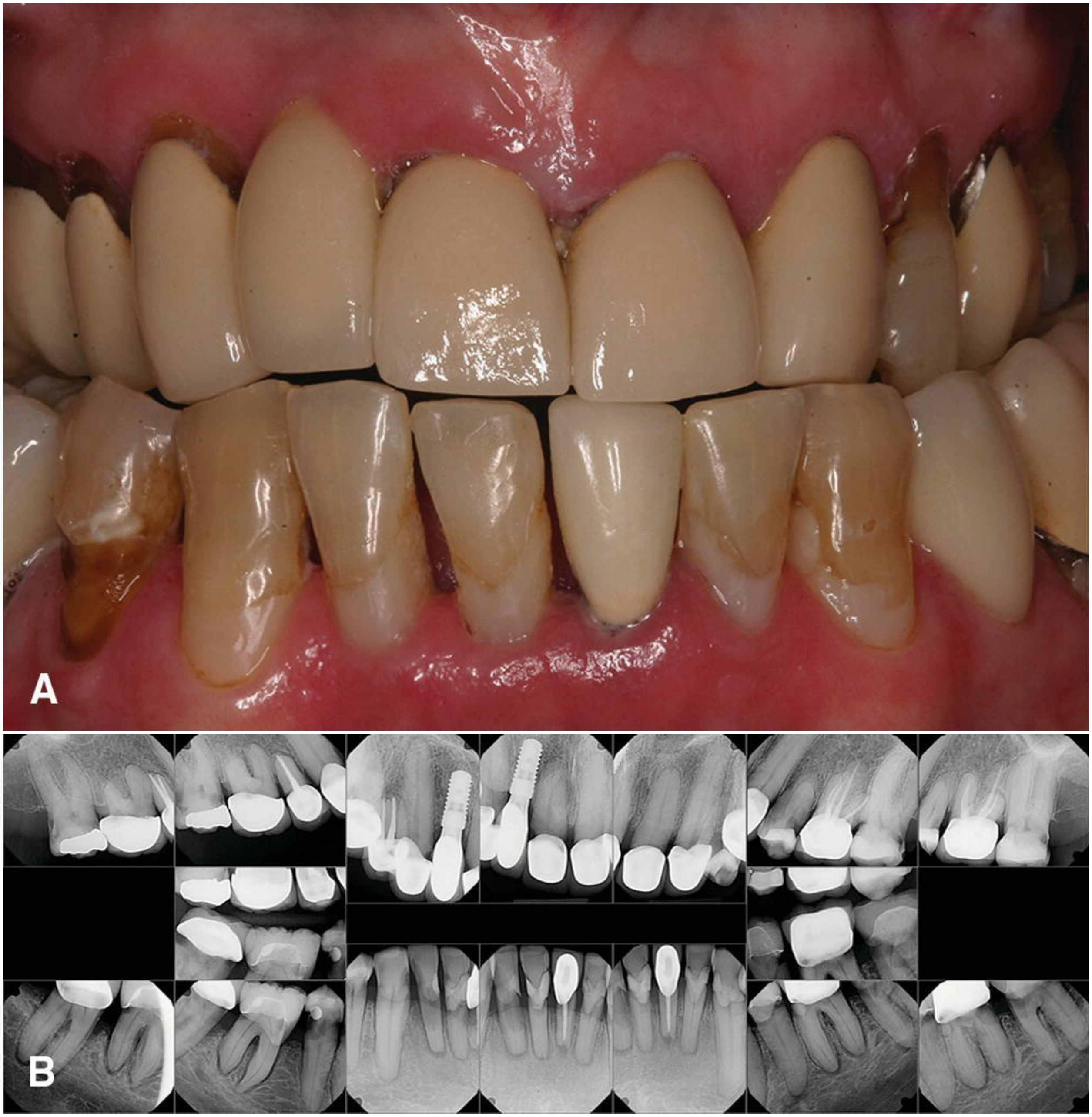


Figure 29.17. A: Rampant caries following radiation therapy for tonsil SCC; note the large carious lesions at the cervical margins of the teeth. **B:** Showing the same patient radiographically; note multiple apical abscess and rampant caries.

The pathogenicity of radiation therapy administered to salivary glands has been attributed to the cytotoxic effects of this treatment on the secretory cells of the glands.[103] Others have attributed salivary gland dysfunction to the direct effects of radiation on the vascular, myoepithelial, and connective

tissues of the glands.[90,102] Saliva is a complex bodily fluid that consists of multiple small organic molecules, electrolytes, and immunoglobulins that defend the oral cavity from contamination and promote healing. Salivary hypofunction can increase the risk for dental caries, compromise mucosal integrity, and impair chewing and swallowing functions.[1] When the salivary glands are within the radiation field, the risk of irreversible damage due to the cytotoxic effects of the radiation is highly likely, as are the clinical manifestations of xerostomia. Dryness of the mucosal tissues may increase susceptibility to oral infections and lead to difficulty in chewing, swallowing, and speaking.[57,103] Susceptibility to caries is not limited to the dentition within the volume of tissue irradiated; all teeth in the oral cavity are a risk.

An effective combination of oral hygiene, frequent dental follow-up examinations, and appropriate prophylactic treatment procedures consisting of flossing, tooth brushing, and fluoride therapy is essential to caries prevention. A daily fluoride program can decrease postradiation dentinal hypersensitivity, remineralize cavitated enamel matrices, and, more importantly, inhibit caries-forming organisms.[1,55] Fluoride treatment should consist of a daily application of 0.4% stannous fluoride or 1.1% sodium fluoride applied to the dentition using a brush-on technique or gel-filled trays (i.e., fluoride carriers) (**Fig. 29.18**).[1,55,90,91] Compared with sodium fluoride, stannous fluoride is slightly more acidic, and as a result, the uptake into the enamel matrices is four times greater.[1,55] Also, the acidic nature of the fluoride may have an antibacterial effect.

Figure 29.18. Fluoride carrier; made of polypropylene. Used to apply fluoride to the teeth. Note the extension beyond the gingival margin of the teeth.

In adults with xerostomia, fluoride leaches out of the enamel within 24 hours; thus, the fluoride regimen must be performed daily for optimal protection. The most efficient method of fluoride application is the use of a custom-made polypropylene fluoride carrier that completely covers, and extends slightly beyond, the tooth surface.[55] Patients fill the carriers ~1/3 full with fluoride gel and place them onto the dentition daily for 10 minutes.[1,55] Patients who receive low doses of radiation and who are expected to have a slight degree of xerostomia can use a toothbrush to apply the fluoride gel.[104] Sensitivity and pain are common adverse effects of fluoride and may necessitate a change in the fluoride concentration or the method of application.

Trismus

When the muscles of mastication are within the volume of radiated tissue, ensuing consequences can lead to restricted mouth opening secondary to

cumulative deposition of fibrous tissues within the muscles, commonly referred to as trismus. There is limited well-structured research surrounding this topic. A limitation in mandibular range of motion, or trismus, can in turn lead to difficulty eating, poor oral hygiene, and impaired speech and limit dental intervention[105] (**Fig. 29.19**).

Figure 29.19. Maximum opening in a patient with severe trismus as a result of maxillectomy and radiation therapy. This patient has difficulty maintaining oral hygiene and inserting the obturator.

Although there is evidence to suggest that the degree of trismus is dose related, detailed correlations between clinical impairment and specific radiation dosages have not yet been established.[106] The incidence of trismus has been reported to range from 0% to 100%.[107] The large variation has been attributed to the lack of uniform criteria and grading scales for trismus, as well as a lack of standardization in assessment style, that is, interincisal measurements versus visual estimation measurements.[107]

Several treatment options for trismus have been proposed; however, there

is limited well-structured research on their efficacy. Most of the regimens include a device to aid in stretching. Devices as simple as tongue blades and unassisted and finger-assisted stretching exercises[108,109] to more complex devices, such as Jaw Dynasplint System[110] (JDS) and Therabite Jaw Motion Rehabilitation System[111] (TJMRS), have been described in the literature. These devices can be generally classified into passive or active motion, depending on whether the muscles of mastication are not involved or involved in opening and stretching of the mandible, respectively. The implementation of an oral physical therapy plan to prevent trismus during and soon after radiation therapy is important to prevent the long-term effects of fibrous tissue deposition in the muscles of mastication, which lead to trismus. Additionally, oral stretching needs to continue lifelong given the cumulative nature of muscle fibrosis after radiation therapy. The effectiveness of oral physical therapy for the treatment of trismus long after radiation has been completed is more limited

A recent study has suggested that trismus is not related to the radiation dose or location but most likely the TGF B1 beta genotype. Development of trismus was significantly related to the presence of the T allele. Although this was a small study of ~60 subjects, this may further the concept of personalized medicine and allow for a predictive model for development of trismus following radiation therapy.[112]

Xerostomia

Radiation therapy can permanently decrease salivary flow. In a study of patients followed for up to 25 years after radiation therapy, Liu and coworkers found that, compared with a nonirradiated group, patients who received bilateral ionizing radiation therapy involving the major salivary gland tissue exhibited, over time, mean decreases of 81% in stimulated and 78% in unstimulated salivary flow.[102] Patients who received unilateral radiation therapy involving only one parotid and one submandibular gland experienced mean decreases of 60% in stimulated and 51% in unstimulated salivary flow.[102] Correspondingly, there is an overall decrease in xerostomia when uninvolved salivary glands are spared during radiation treatment. Patients who underwent cervical with supraclavicular radiation therapy (i.e., mantle field treatment) experienced mean decreases of 43% in stimulated and 32% in unstimulated salivary flow.[102]

Radiation-induced reductions in salivary flow are worrisome because saliva protects the oral mucosa from dehydration and assists in the mechanical lavage of food and microbial debris from the oral cavity.[103] To avoid oral infections and to reduce the mucositis that may arise from radiation therapy, patients must frequently rinse the oral cavity to reduce oral microorganisms and to maintain mucosal hydration. Such oral lavage can be performed by rinsing with a solution of 1 tsp of sodium bicarbonate dissolved in 1 quart of water several times each day to alkalinize the oral cavity and keep the oral and oropharyngeal tissues moist.[1,37]

The traditional treatment for radiation-induced xerostomia is inadequate because no salivary substitute for patients with these conditions can replicate natural salivary mucin and protective salivary components.[48,55] Mouth rinses, saliva substitutes, and gustatory stimulants are frequently abandoned by patients treated with head and neck radiation therapy, but these can aid in palliating xerostomia. Such patients should be encouraged to increase their intake of water, decrease their intake of acidic and carbonated beverages, and decrease their intake of sodium during treatment. Sialagogue therapy, such as with cholinergic agonists (e.g., pilocarpine hydrochloride), has been shown to provide clinically significant relief of symptoms of postradiation xerostomia.[113,114] Healthy oral tissues can be maintained following radiation therapy. Success depends not only on careful oral planning but also on the patient's cooperation and compliance.

Intensity-Modulated Radiation Therapy

One advance in radiation therapy has been the introduction of computed tomography (CT) to define tumor volumes and normal tissues for the development of radiation beam arrangements.[115] The process, known as three-dimensional conformal radiation therapy, enables a higher dose to be directed at the tumor while minimizing the effects on normal tissue. Another advance in technology in radiation oncology is intensity-modulated radiation therapy (IMRT), a technique that delivers radiation more precisely to the tumor while sparing the surrounding normal tissues.[116] IMRT also allows inverse planning and computer-controlled radiation deposition and normal tissue avoidance (i.e., parotid-sparing techniques).[116] IMRT has wide application in most aspects of radiation oncology because of its abilities to create multiple targets and multiple avoidance structures, to treat different

targets simultaneously at different doses, and to weight targets and avoid structures according to their vital importance. IMRT is an approach to conformal therapy in which high-dose radiation is administered to target volumes whereas lower-dose radiation is delivered to sensitive structures. With certain head and neck treatment schedules, IMRT may reduce the total dose to major salivary glands, thereby decreasing the incidence and severity of postradiation-induced xerostomia.

Intensity-Modulated Proton Therapy

Intensity-modulated proton therapy (IMPT) was recently introduced for the treatment of head and neck cancer. It is thought to be superior to IMRT given the proton's physical property to stop at the targeted range of the tumor, thus limiting the amount of normal tissue radiated (i.e., Bragg peak).[117] By reducing the dose intensity to normal tissues, IMPT is associated with a reduction in the oral morbidities associated with radiation therapy contributing to an overall increase in quality of life during and following treatment.[117] Randomized blinded clinical trials are currently underway to further determine the differences between IMPT and IMRT in regard to radiation treatment–associated oral morbidities, including salivary flow (both stimulated and unstimulated) and oral opening.

CHEMOTHERAPY

Today, many patients with cancer of the head and neck receive chemotherapy as a single- or multiple-drug regimen, either alone or in combination with other therapies.[76,118–121] The duration of treatment ranges from several months to years, depending on how long the therapy remains effective or how long the patient can tolerate it. Most chemotherapeutic agents are designed to kill multiplying tumor cells but also target mitotically active normal tissue cells, and therefore, chemotherapy often induces toxicity in the hematopoietic cells, skin/mucosa, and aerodigestive tract.[37,76] Such toxicity may cause treatment-induced complications in the oral cavity, especially if myelosuppression has occurred. Many of the sequelae of chemotherapy are similar to those induced by radiation therapy, but sometimes, they are more episodic in relation to the chemotherapy regimen owing to the dosing schedule or agents administered.

Oral Complications from Chemotherapy

Treating oral conditions resulting from chemotherapy is interesting and challenging for the oral oncologist. The medical team often experiences anxiety over precipitating oral problems during therapy, and patients, after reading the literature addressing the sequelae of chemotherapy, are sometimes overtly fearful of the complications (e.g., fear that brushing the gingival tissues can result in a septic condition).[1,37,122] Thus, a regular regimen of dental visits and good hygiene practices is replaced with suboptimal oral care practices.

Acute oral conditions detected during the oral and dental evaluation of patients with cancer must be treated before chemotherapy if the patient's health or hematologic values permit or, if not, when the opportunity arises between treatment cycles and an appropriate performance status has been established. Chronic problems should not go unattended but should be treated strategically as the patient continues with chemotherapy.[37] With appropriate coordination, acute problems can be treated promptly. If left untreated, chronic conditions may become acute at a time when the patient's physical well-being or hematologic parameters will not allow oral treatment intervention.

Dental practitioners must not lose sight of the long-term medical and oncologic goals for patients with cancer; additionally, they must not implement elaborate restorative plans or treat periodontal conditions that would have a guarded prognosis in patients without cancer.[121] During oncologic therapy, the oral treatment plan for patients with cancer should be simple, practical, and functional in relation to the patient's oral or dental health and should not be in the realm of cosmetic dentistry; extensive, complex fixed prosthodontics; or advanced periodontal therapy.[37,123] Dental specialists face an almost overwhelming temptation to give esthetic possibilities undue consideration while failing to recognize the difficulty patients face in coping with their cancer diagnosis and undergoing drug therapies that have serious adverse effects.[1,37,45]

Oral Infection

Even before the initiation of chemotherapy, individual malignancies can predispose individuals to infectious risks, with neoplastic processes of either

bone marrow or lymphoid tissue (i.e., lymphoma) having the greater potential for infection.[124–126] The risk for infection further increases after treatment has started and is compounded for patients at more advanced stages of the therapeutic regimen or with more advanced stages of disease.[37]

Oncologic therapy designed to control or cure disease and to prolong survival can severely weaken the immune system, creating excellent conditions for infection to develop locally or to become a septic focus.[127,128] Despite major preventive practices such as prophylactic antibiotics, isolation techniques such as protected environments, and treatments such as immunologic leukocyte growth factors, the immune system can be immensely impaired by both the malignancy and the therapeutic regimen used to control infection. Even more challenging is the potential or presence of an existing infection that can be manifested by a broad spectrum of clinical signs and symptoms owing to a severely impaired immune response or the common use of prophylactic rather than therapeutic antibiotic, antifungal, or antiviral agents during treatment. Oral complications associated with cancer and its therapy have been well documented and are broadly categorized as infection, mucositis, or bleeding problems.[23,129]

Given the immunosuppressive effects of malignancy and its treatment, empirical use of an oral decontamination agent, that is, 0.12% chlorhexidine gluconate and 1.1% sodium fluoride toothpaste, may substantially lower the risk of infection of the oral cavity and alter the presenting signs and symptoms of infection during chemotherapy.[37] Oncologists and treatment centers vary in their treatment philosophies on the use of such anti-infectious agents. The dentoalveolar complex should be thoroughly evaluated for microbial reservoirs (e.g., plaque, calculus, or periodontal pockets), and these infectious foci should be eliminated before the start of chemotherapy (**Fig. 29.20**).[23,37] A compromised periodontal status increases risk of infection.[130,131] Clinically, however, the risk of infection depends on multiple interacting factors, such as oral hygiene status, immune-myelosuppressive status, chemotherapeutic agents used, prophylactic or therapeutic antimicrobial agents used, and the degree of periodontal disease.

Figure 29.20. Severe gingivitis causing significant inflammation and increased risk of bleeding. These inflamed areas are portals of entry for bacteria potentially causing systemic infections and are bleeding risk sites.

Oral Care.

To minimize the risks of oral infection, it is important that simple and practical guidelines be developed for maintaining oral health and for diagnosing, preventing, and treating oral–periodontal infection during therapy.[1,37] Patients with cancer should make regular dental visits for overall dental and periodontal assessment. Patients receiving chemotherapy can undergo a dental treatment provided that they meet the following hematologic conditions: (1) an absolute neutrophil count of ~1,000/mm^3 (white blood cell count times percent neutrophils equals the absolute neutrophil count), a level at which the risk of developing an infection is minimal, and (2) a platelet count above 50,000/mm^3 with a normal coagulation profile.[79] The administration of prophylactic antibiotics is essential owing to the induced bacteremia, immunocompromised status, and potential for hypofunctioning white blood cells introduced by chemotherapy. The American Heart Association recommends that a viable antibiotic regimen to prevent subacute bacterial endocarditis be administered before periodontal procedures.[132,133]

Patients with an uninfected dentition and good periodontal health do not pose a treatment challenge, nor do patients with mild periodontal disease that

does not mandate immediate surgical intervention. However, patients with increased loss of attachment from resultant bone loss with root exposure or periodontal pocket formation pose a treatment dilemma.[37] Patients in whom pocket depth is normal (between 1 and 4 mm) can be treated with regular periodontal care and maintenance, even though there has been a history of periodontal disease. Extraction should be considered only for patients with pathologic mobility of dentition or fulminant periapical abscess.[1,37]

Patients with moderate to advanced periodontal disease present a greater challenge and would, under usual circumstances, receive instructions for infection prophylaxis and dental hygiene, as well as surgical intervention; however, the feasibility of such comprehensive therapy during chemotherapy can be limited by several factors, including performance status, type of malignant disease, cycling of chemotherapy, and hematologic competence. The clinician should strive to provide a thorough scaling/root planing and to encourage maintenance through exceptional plaque control (i.e., tooth brushing, flossing, and use of antimicrobial mouth rinse).[37,134,135]

To reduce the risk of septic foci, extractions should be considered for patients with an exacerbated or acute periapical infection. This oral surgical correction should be performed at the appropriate time in the treatment cycle or when the patient's cancer is in remission. If chemotherapy is on hold, oral–periodontal surgery could be considered provided that the hematologic status is appropriate. The oral oncologist must discuss with the treating medical oncologist about the patient's oral status, treatment plan, and contraindications to surgical intervention, as well as the appropriate timing of oral procedures.[37,76,118]

Periodontal Care.

Tooth brushing and flossing should be the standard of dental care. As in the general population, many patients with cancer either do not floss or floss only infrequently; therefore, clinicians may either instruct patients to floss or stress its importance. If the clinician identifies an area in which food continually lodges, the patient should be encouraged to floss the area to reduce the risk of gingival inflammation.[45]

Patients who floss regularly are instructed to modify the flossing technique in certain clinical situations: First, patients are instructed to floss gently when the lining of the oral cavity starts to become sensitive to thermal

changes or food substances, indicating mucosal thinning due to suppressive effects of chemotherapy on the normally proliferative epithelium.[82] Second, patients are instructed to floss only to the gingiva when the platelet count is above 50,000/mm^3. This technique removes most of the debris from the teeth. By not flossing at all, about half of the teeth are not cleansed.[37]

Brushing the teeth is imperative for plaque control. The patient should be instructed to brush after each meal. In certain clinical situations, such as increased mucosal sensitivity to food or thermal changes, increased sensitivity to toothbrush bristles, irritation of the gingival tissues by the toothbrush, or profound thrombocytopenia (<20,000/mm^3), patients should change from a soft to an ultrasoft-bristled or sensitive-bristled toothbrush.[1,37,45,59]

In controlling plaque accumulation, it is important that the risk of gingival inflammation be minimized, along with the oral bacterial load and the potential for infection.[136] Along with routine brushing and flossing, rinsing with chlorhexidine gluconate should be initiated when patients begin chemotherapy. Such rinsing is an adjunct to ideal oral–periodontal care and can also be used when indications arise, such as oral mucosal changes secondary to chemotherapy and subsequent increased soft tissue sensitivity.[37,134,135] Patients undergoing chemotherapy should be encouraged to rinse with a dilute saline and sodium bicarbonate solution (5%) to reduce adherent mucoid debris on oral soft tissues, to lubricate oral mucosal and oropharyngeal tissues, and to elevate the pH of oral fluids.[45] Patients who experience nausea and anorexia should be encouraged to rinse with the sodium bicarbonate and salt water solution several times throughout the day to reduce oral acidity and minimize the mucosal insult.[137,138]

Another challenge cancer patients face is the risk of local infection or septicemia associated with dental implants. If an implant with its restorative component poses a risk of infection for patients under normal circumstances, this risk will be intensified during chemotherapy. Interventional antibiotics and aggressive hygiene have limited ability to control infection caused by a poorly integrated endosseous implant, whereas a well-integrated implant should not pose problems if its integrity is maintained with effective dental hygiene practices.[49–51]

Aggressive anticancer therapy severely undermines the integrity of the

mucosal epithelium of the oral cavity. In addition, the oral cavity is a focused area for trauma from teeth, denture prostheses, and hot or cold dietary substances.[4] Many patients are at risk for infection from resident microflora or opportunistic pathogens sequestered in sanctuary areas (**Fig. 29.21**). Furthermore, cancer patients share with the general population common problems of the oral cavity, such as poor hygiene, poorly maintained dentition, periodontal disease, prostheses in poor repair, as well as the associated mucosal disease.[37] With all these interactive injurious influences in such close proximity, even small alterations in the area can cause a problem. Each course of chemotherapy introduces this threat of oral complication, and the risk of developing complications with subsequent courses increases as local or systematic resistance is challenged. Appropriate evaluation of the oral cavity and correction of existing oral and dental pathology can minimize, and in some cases eliminate, treatment-limiting toxicities such as mucositis, oral infections, and bleeding that necessitate dose reduction or termination of chemotherapy.[4,76,139]

Figure 29.21. Patient undergoing chemotherapy; significant pain is noted due to an overgrowth of Candida. Diagnosis is confirmed with culture and sensitivity testing.

Chemotherapy-Induced Mucositis

The oral mucosal response to chemotherapy is varied and unpredictable. Some patients undergo the most aggressive treatment regimens with no problems; others experience increased mucosal sensitivity to food and thermal changes due to the thinning of the mucosal epithelium or profound ulcerative lesions. These soft tissue mucosal reactions can confuse treating physicians, leading to inappropriate local oral treatment parameters and substantially influencing whether chemotherapy is continued.

Diagnosis.

Oral mucosal reactions must be identified as either stomatitis or mucositis;

the distinction determines the treatment and provides insight into the overall effectiveness of the chemotherapeutic regimen.[1,37,43,45] A diagnosis of oral stomatitis should be made when the integrity of the mouth has been altered by traumatic events, such as a coarse diet, an ill-fitting denture prosthesis, or infectious agents (i.e., viral, bacterial, and fungal). In contrast, a diagnosis of oral mucositis should be reserved for oral tissue changes that are the direct cytotoxic effects of chemotherapy. All other factors must be ruled out before a condition is diagnosed as mucositis. An incorrect diagnosis of mucositis could cause unnecessary delay, reduction in dose, or complete discontinuance of potentially effective chemotherapy. Incorrect mucosal assessment can also lead to improper care and treatment and thus to the persistence of the mucosal disease.[37] This problem can be further compounded by superinfection, pain, decreased nutritional intake, bleeding, or a focus for sepsis, effects that increase the treatment morbidity, treatment costs, length of hospital stay, need for additional antibiotic therapy, and need for parenteral nutritional support. Stomatitis is preventable, and the condition can be corrected or significantly reduced with antimicrobial or dental therapy such as correction of a plunger cusp causing frictional irritation of the lateral tongue and subsequent ulceration and marked discomfort.

Etiology and Progression.

Patients vary considerably in their tolerance of various chemotherapy agents and the development of mucositis. Chemotherapeutic agents (e.g., antimetabolites, alkylating agents, and vinca alkaloids) known to produce mucositis may not produce a mucosal reaction when given at the appropriate dose and duration, whereas other agents not known to produce mucositis, if given at an intensified dose or for a sufficient duration, can produce mucosal toxicity, thus necessitating dose reduction.[22,82,140]

Mucositis, the most common acute complication of chemotherapy, has a specific, defined mechanism of progression: Mucosal erythema progresses to oral sensitivity and then to mucosal denudation.[3,22,82,140] Several grading scales for oral mucositis have been developed to assess the severity of the mucosal reaction during each course of chemotherapy. Grading scales range from the simple to the complex.[23,141–144] A universal grading system for mucositis has not been established and accepted by the profession.

The most commonly used scale to assess mucositis severity was the

World Health Organization (WHO) classification (1 = soreness, erythema; 2 = erythema, ulcers, can eat solids; 3 = confluent ulcers, requires liquid diet only; 4 = oral alimentation not possible, hemorrhage) although it is used in less than one-half of all studies. The RTOG oral mucositis grading system incorporates both a patient-graded component and an assessment by a medical professional (1 = erythema; 2 = patchy mucositis; 3 = greater than one-half of the mucosa affected by a fibrinous mucositis; 4 = necrosis and hemorrhage, functional component graded by patient). Validity and reliability have yet to be established with this grading scales and this, in turn, may lead to difficulty in interpreting result of clinical trials or systematic reviews. The National Cancer Institute (NCI) first created the Common Toxicity System (CTC v1.0) in 1983 to aid in the recognition and grading of adverse chemotherapy events. Since that time, several versions have been introduced. The CTCAE 4.0 scale is the most updated version of their Adverse Events (AE) (1 = erythema; 2 = patchy ulcerations or pseudomembranes; 3 = confluent ulcerations, bleeding with minor trauma; 4 = issue necrosis, significant spontaneous bleeding, life-threatening consequences; 5 = death). Validation studies are currently being undertaken.

In cases of appropriately diagnosed mucositis, the emergence of mucosal toxicity would be expected to coincide with the administration of chemotherapy. However, mucosal HSV infections occurring early in the chemotherapy cycle can mimic mucositis. Failure to collect diagnostic cultures with each mucosal reaction can lead to a misdiagnosis of mucositis, in which the infection goes untreated.[145–149] Culturing at this early stage of therapy is essential for differentiating mucositis from infectious stomatitis, which can be caused by a bacterial, fungal, or viral agent and which is usually associated with a low neutrophil count.[1,37] Oral mucosal infectious agents must be correctly identified and treated because the loss of mucosal integrity creates a portal of entry for systemic infection in immunocompromised patients.[129]

Chemotherapeutic Agents Associated with Mucositis.

Chemotherapy-induced pancytopenia, combined with mucositis, can cause oral infection and bleeding events. Severe thrombocytopenia (platelets < 20,000/mm^3) and neutropenia (neutrophils < 500/mm^3) may be present despite normal-appearing oral mucosa. Serious complications, such as

hemorrhagic diathesis or sepsis, can occur if hematologic parameters are not considered in the treatment of the oral cavity. Thus, clinicians should conduct a benefit-versus-risk analysis of the intended therapy and should thoroughly assess the hematologic values before each treatment intervention. Treatment guidelines based on such assessments have been established.[1,3,23,37,150]

Drug-related mucositis can be severe, with onset occurring within 7 days after initiation of chemotherapy and with duration varying from several days to weeks. Compared with single-agent therapy, combination drug therapy or chemoradiation therapy is more likely to intensify mucosal morbidity. Maximal myelosuppression can induce thrombocytopenia, thereby causing gingivitis and gingival bleeding.

Drugs most frequently associated with mucositis and myelosuppression include Cytoxan, etoposide, cyclophosphamide, doxorubicin, dactinomycin, daunorubicin, 5-fluorouracil, bleomycin, melphalan, and methotrexate.[3,16,25,32,76,80,118,121,138] Chemotherapy is usually administered over 3 to 5 days, and recovery intervals of 21 to 28 days are usually provided between chemotherapeutic sessions.[37,123] Drug-induced myelosuppression renders patients susceptible to hemorrhage and increased infectious potential.[138]

Targeted Therapy.

As cancer becomes more targeted and personalized, new systemic therapies have evolved; these agents are specific to pathways and molecules involved in carcinogenesis. Because of their specificity, some of the oral complications and myelosuppression are less than those with traditional cytotoxic chemotherapy. Epidermal growth factor receptor (EGFR) inhibitors are one of the recent additions to this class of drugs. The most common adverse reaction with EGFR inhibitors is cutaneous reaction, usually treated with antibiotic creams. Cetuximab is an EGFR inhibitor that is currently approved for locally advanced cancer of the head and neck and has been found to be superior to definitive radiation therapy alone when used in combination with radiotherapy.[151] Oral mucositis associated with cetuximab presents with generalized erythema and is less ulcerative than is typically seen with traditional cytotoxic chemotherapy.[152] When a targeted therapy and cytotoxic agents are used together, a combined presentation of oral mucositis is seen in which the classic presentation is aggravated by a generalized erythema

extending to the labial mucosa (**Fig. 29.22**).[152] Bonner et al. in 2006 found similar oral toxicities with radiation therapy alone versus concurrent chemoradiation with cetuximab, whereas a retrospective review with a meta-analysis found an increased prevalence of mucositis in patients receiving concurrent radiation therapy with cetuximab versus concurrent radiation therapy with traditional cytotoxic therapy. Further assessment is required given that oral toxicities are often not mentioned in clinical trials.

Figure 29.22. Patient undergoing concurrent chemoradiation with cetuximab for nasopharyngeal CA. **A:** Note the generalized facial rash associated with EGFR inhibitors. **B:** Note the mucositis present with generalized erythema, which is less ulcerative than what is typically seen with traditional cytotoxic chemotherapy.

Treatment.

Unlike the approach to oral stomatitis, effective therapy for oral mucositis has not been standardized. The MASCC, in partnership with the ISOO, in 2013, extensively reviewed the literature on treatments for the chemotherapy-induced mucositis. Cryotherapy (cooling therapy) was found to be effective for bolus chemotherapy regimens with short half-lives.[87] Keratinocyte growth factor-1 (KGF-1) was found be successful in autologous stem cell transplantation if given 3 days before the conditioning regimen.[88] There was insufficient evidence to support the use of amifostine in the prevention of oral mucositis.[89] Most interventional agents are aimed at either the prevention/reduction or the palliation of toxicity caused by chemotherapy. The many agents used vary widely in their mechanisms of action.[140] In cases of mucositis that can be controlled, chemotherapeutic agents, alone or in

combination regimens with mucositis medication, are escalated to higher doses to achieve the ultimate goal of cure of cancer. Gingival hemorrhage can usually be controlled by local measures such as the application of pressure, cool water, periodontal dressings, topical thrombin, gelatin sponges, oxidized cellulose, prefabricated stents lined with a hemostatic agent, or tranexamic acid.[1] Persistent hemorrhage may require platelet support.[16,21,37]

Antibiotic and Diet.

Any emergent oral treatment given while patients undergo myelosuppressive chemotherapy requires prophylactic antibiotic coverage, and all patients with indwelling central venous catheters require prophylactic antibiotic coverage for procedures likely to induce bacteremia.[45] The oral oncologist should consult with the patient's treating oncologist for the selection of the most appropriate antibiotic.

Although grossly overlooked, diet profoundly influences the stability of the oral tissues and can cause mucosal problems when a patient is undergoing chemotherapy.[1,118] During the myelosuppressive phase of therapy or when the mucosa is thinned owing to chemotherapy, the diet should consist of nontraumatizing, soft foods that reduce the risk of puncture, abrasion, or damage to the compromised mucosal epithelium. Hard or abrasive food items can lead to increased pain, infection, or bleeding episodes. All sources of trauma should be minimized or avoided completely.

Patients at Higher Risk.

Viral reactivity may lead to severe oral or disseminated infection during periods of immunosuppression. In particular, HSV infections are often associated with severe, painful, and prolonged ulcerations atypical of those found in immunocompetent hosts (**Fig. 29.23**).[26,145–148] Suspected HSV lesions should be treated with antiviral agents such as acyclovir administered orally or intravenously and should be managed as described earlier for irradiated patients. The diagnosis should be established with the use of viral cultures, direct immunofluorescence, or other rapid diagnostic tests, as well as histologic assessment of the lesions.[26,145–148]

Figure 29.23. Culture-positive HSV oral infection is treated with antiviral systemic and topical medications.

Bacterial infection following chemotherapy can cause localized mucosal lesions, sialoadenitis, periodontal abscesses, pericoronitis, or acute necrotizing ulcerative gingivitis.[37,121] Because systemic infection is a serious complication in neutropenic patients, constant vigilance must be maintained

to prevent or manage oral infection of any type.[1,11,37,45] Oral infection should be treated with selected antibiotic combinations (broad-spectrum antibiotics), including an agent effective against anaerobic Gram-negative bacilli such as *Pseudomonas* species, *Klebsiella* species, or enterobacteria, which are often found in the oral cavity of immunocompromised individuals.[37,45,121] Oral microbial culture testing should be used to ensure antibiotic sensitivity and resistance selection and to assist in identification of causative organisms.[37]

PROSTHETIC REHABILITATION AFTER HEAD AND NECK CANCER TREATMENT

Self-confidence can be decreased in patients that have undergone head and neck cancer therapy, particularly those who have undergone ablative surgical resection. Intra- and extraoral prostheses restore form and function, in turn, lessening the challenges associated with cancer therapy and improving patient's overall quality of life.

Maxillary Defects

The oral–nasal defect resulting from a maxillectomy procedure leads to unintelligible speech, impaired swallowing, and nasal regurgitation, unless oral–nasal separation can be reestablished. This can be accomplished surgically, with a flap reconstruction, or prosthetically with an obturator. An obturator is a removable prosthesis that replaces the missing portion of the palate that has been resected during the tumor-ablative surgery.[153] The obturator functions primarily as the partition between the oral cavity and the sinonasal cavity and secondarily to recreate the palatal contours for appropriate speech sounds.[154,155] Size and location of the surgical defect and presence and condition of remaining teeth are considerations for prosthetic rehabilitation.[154] As the size of the defect increases, the number of remaining teeth and amount of residual palatal decreases, which, in turn, reduces stability, retention, and support of the obturator prosthesis.[154–157] This, then, decreases functionality overall and thus patient satisfaction.[157–159]

Osseointegrated endosseous implants placed in edentulous areas provide

retention and stability to prostheses that otherwise would be compromised due to lack of tissue-bearing surface.[155,160,161] Important factors in the successful implant prosthetic rehabilitation following radiation therapy are similar to that of nonradiated patients, that is, fixture and abutment length and appropriate selection of implant sites. However, in a patient with a history of radiation therapy, radiation dose to proposed implant sites and time from radiation therapy to implant surgery requires significant consideration.[72,155,156] As the amount of radiation increases to a proposed implant site, the risk of ORN also increases. It has been suggested that HBO therapy reduces this risk; however, the use of implant-born prostheses in radiated patients remains controversial and is actively being studied.[162]

Difficulties in prosthetic rehabilitation can be minimized, or even eliminated, with careful surgical planning. Dental casts are usually fabricated presurgically and used for discussion between the head and neck surgeon and the maxillofacial prosthodontist. The proposed surgical margins should be established so that an appropriately sized prosthesis can be fabricated. The overall oral condition should be addressed, that is, oral surgical needs and dental restorations that may be required. Teeth that are nonrestorable or have questionable prognoses require extraction, ideally at the time of surgery.[155]

Several surgical enhancements can be incorporated in order to improve the outcome of the prosthesis.

1. Osteotomies between teeth should be avoided; rather, it should be made through either an edentulous area or the socket of an extracted tooth in order to prevent bone/tooth loss.[155]
2. A split-thickness skin graft (STSG) should be placed in the maxillary defect over any exposed bone and at the cut edge of the buccal mucosa. This will allow for formation of a scar band, which will provide retention of the obturator and create a prosthesis-bearing surface.[72,155–164]
3. Removal of the inferior turbinates, even if unaffected but tumor, is recommended to allow for adequate superior extension of the prosthesis. The respiratory epithelium surrounding the turbinates is friable and will become a constant source of bleeding and irritation.[72,155,156,160]
4. The amount of remaining maxilla will directly influence the support and stability of the prosthesis. Sparing prosthesis-bearing areas, that is, the tuberosity bilaterally and the premaxilla, will increase functionality of

prosthesis and most likely patient acceptance.[72,155,156,160] The remaining palatal mucosa can be wrapped around the palatal aspect of the osteotomy to provide a denture-bearing surface.

5. An intraoral approach is recommended when possible, as opposed to a Weber-Fergusson incision. This allows for ease of manipulation of the lip and cheek postoperatively during the interim phase of obturation.[160,163]

Surgical Reconstruction of Maxillary Defects

Current microvascular techniques have facilitated surgical reconstruction of a maxillectomy defect, thus effectively restoring function and cosmetics. However, depending upon bulk, type of graft, and location of reconstruction, it may preclude future prosthetic rehabilitation. If the flap invades the space where the prosthetic teeth should be, prosthetic rehabilitation may not be possible without revising the flap (**Fig. 29.24A and B**).

Figure 29.24. A: Maxillary defect immediately following reconstruction; note lack of restorative space and lack of vestibule. **B:** Same patient following revision and implant placement. Note sufficient space for prosthetic teeth.

An osseous element is often necessary for successful prosthetic rehabilitation following surgical reconstruction of the maxilla. This bone provides support for the prosthesis and provides an area for implant placement. The free fibula graft is well suited for this type of reconstruction. The vertical height of a fibula has been found to range from 13.1 to 16.7 mm, with an average of 15 mm.[164–166] The adequate stock of bone, along with bicortical configuration, is ideal for placement of endosseous implants (**Fig. 29.25**). Many bone defects in the head and neck are considered suitable for fibula reconstruction and functional rehabilitation can be optimized in these patients. With the addition of CAD/CAM technology, osteocutaneous reconstructions can be planned virtually to include endosseous implants. CAD/CAM implant placement guides can be fabricated allowing implants to be placed into the fibula prior to transfer into the head and neck region. This allows for predictable prosthetic restorations that are implant supported/retained, potentially delivered immediately in some cases.[167–170] Patients who receive implant-retained maxillary prostheses placed into fibula reconstructions have near optimal mastication and speech.[169]

Figure 29.25. Model of endosseous implants placed into a fibula. Note the bicortical stabilization.

Soft tissue flaps, without an osseous component, often lack the ability to support a prosthesis, making for a nonretentive and potentially nonfunctional prosthesis. Alveolar or bone support and relatively immobile soft tissue are key elements in a functional prosthesis. These flaps are thought to best serve patients who are not interested in postsurgical prosthetic rehabilitation and those, possibly, unable or unwilling to care for a traditional obturator.[154]

Prosthetic rehabilitation using obturator prosthesis is divided into three phases: surgical, interim, and definitive.

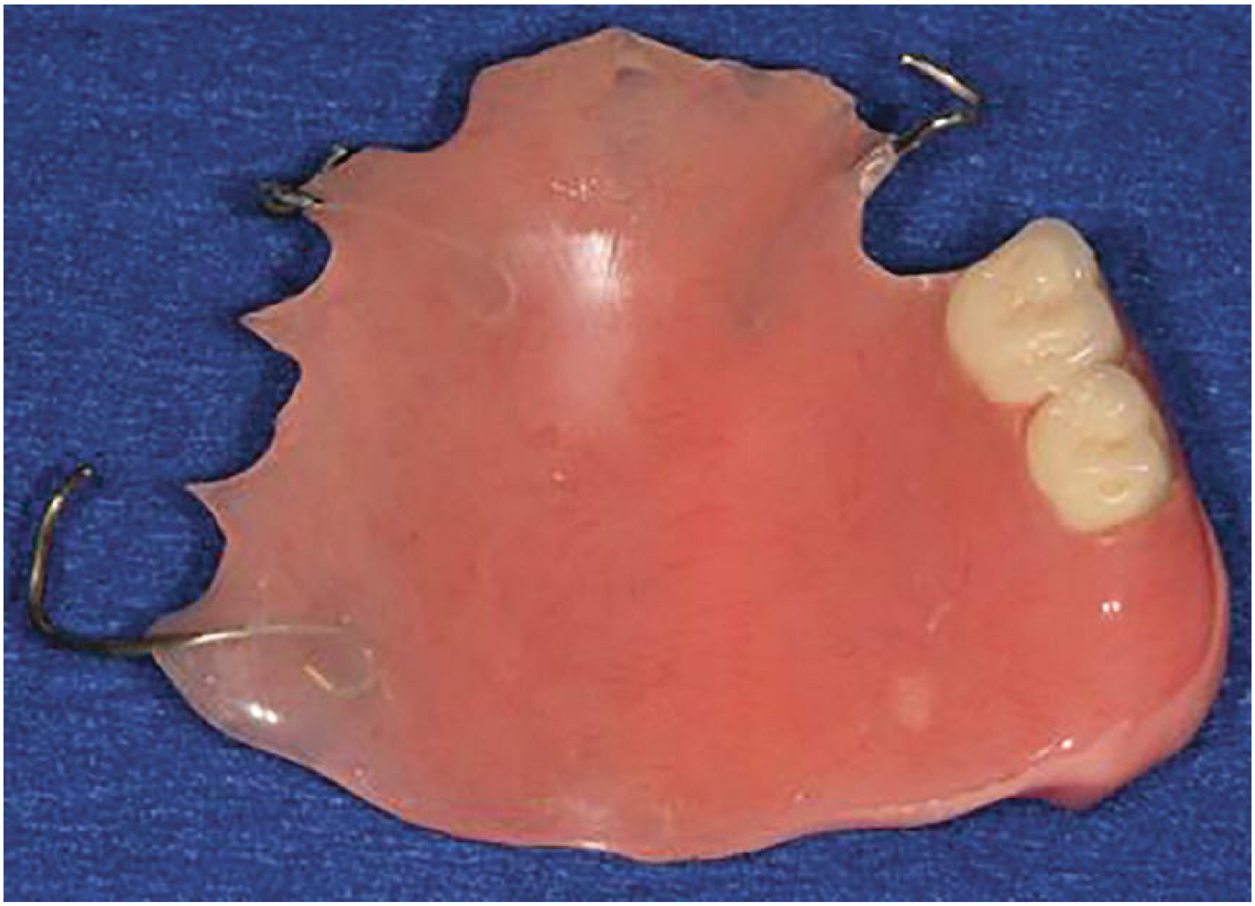
Surgical Obturator

A surgical obturator is a prosthesis, often without prosthetic teeth, placed at the time of surgery. The primary objective of this prosthesis, along with restoring the palatal continuity, is to support the surgical packing, holding the STSG in place. It also reduces risk of postoperative bleeding. Surgical obturators enable early postoperative oral alimentation and, therefore, often bypass the need for a nasogastric feeding tube and decrease the duration of postoperative recovery. Maintaining the patient's ability to eat and speak immediately postoperatively improves patient's psychological status.[154,155,163,168] The surgical obturator most often will not have prosthetic teeth, depending on the situation. It is usually retained by stainless steel orthopedic screws in the edentulous patient and by interdental wrought wire in the dentate patient. For patients who wear prostheses, it is sometimes possible to modify an existing maxillary removable partial denture or complete denture to be used as a surgical obturator.[14] A surgical obturator remains in place for ~5 to 10 days; however, it can remain in place for up to 14 days without problems.

Interim Obturator

An interim obturator prosthesis is placed following removal of surgical obturator/packing, generally 5 to 10 days later. During normal healing, the maxillectomy defect will continue to remodel, leading to ongoing challenges of nasal regurgitation and hypernasality. In order to accommodate these

changes, the interim obturator is modified with resilient polymethyl methacrylate material (**Fig 29.26**). At this point, prosthetic teeth are added to establish appropriate lip and cheek support during healing, increase function, and reduce contracture of scar tissue.[154,155,163,168] A well-contoured, intimately fitting interim obturator can be converted to a definite obturator once the defect becomes dimensionally stable. This prosthesis is worn throughout the cancer treatment phase, that is, postoperative radiation therapy and chemotherapy.



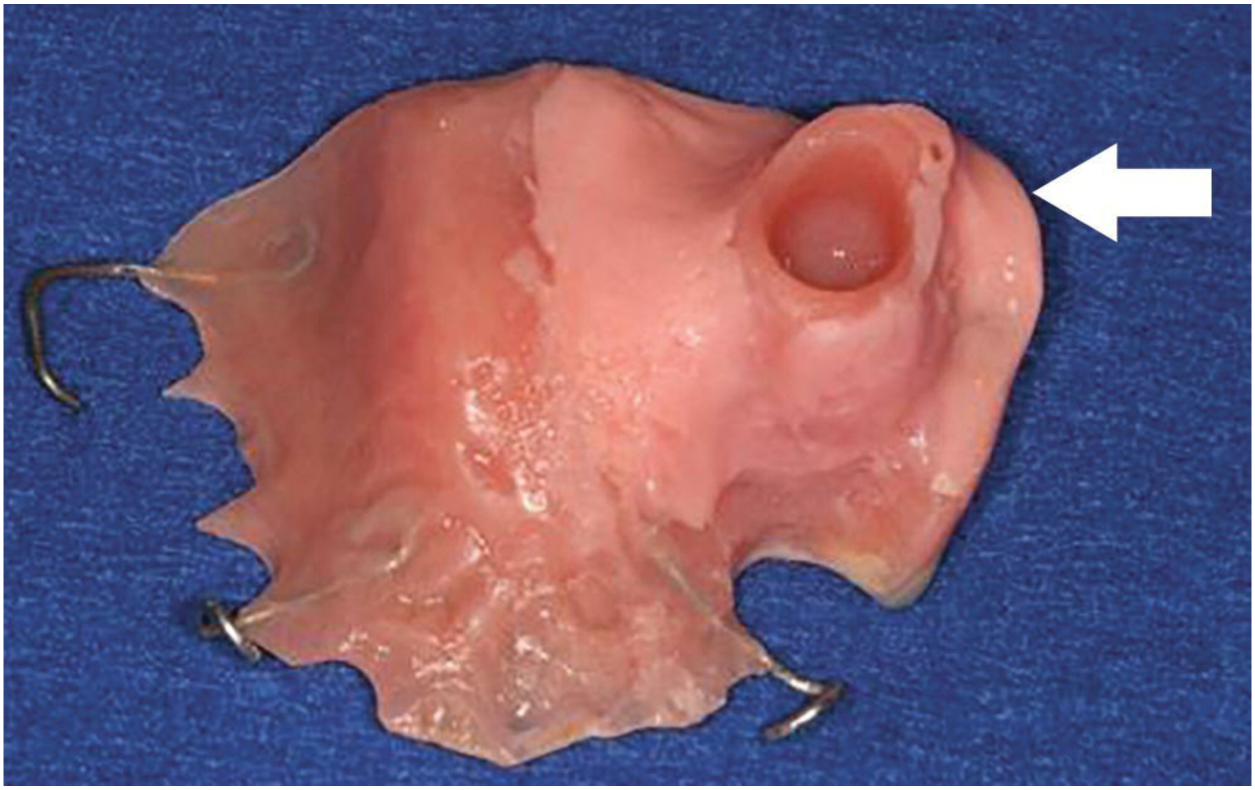


Figure 29.26. Polymethyl methacrylate obturator; the *arrow* indicates soft reline material that is modified to accommodate the healing defect.

Definitive Obturator

A definitive obturator should be fabricated 3 to 4 months following completion of treatment, once the defect is dimensionally stable; however, multiple factors may affect timing of fabrication, that is, size of defect, the use postoperative radiation, prognosis of tumor, severity of oral complications, or progress of healing.[153,154] Missing teeth are replaced to improve oral function and esthetics and restore facial symmetry. These prostheses can be fabricated with a metal framework, fabricated from chrome cobalt, depending upon contours and condition of remaining teeth and patient expectations (**Fig 29.27**). Often, a metal framework is not possible without substantial prosthetic modification to the remaining dentition. As with any maxillofacial prosthesis, the remaining dentition is critical to the functionality of the prosthesis. Every effort should be made to maintain and enhance the dentition.[71,155]

Figure 29.27. Definitive obturator with a metal framework. The definitive phase begins when the defect becomes dimensionally stable. The definitive prosthesis maximizes stability, support, and function.

Information given to the patient regarding prosthetic rehabilitation must be tempered by the experience and judgment of the clinician. Questions concerning the diagnosis and prognosis of the disease should be referred to the primary surgeon in charge of the patient’s overall care. The patient should also be informed of any variables beyond the control of the clinician that may compromise an ideal result. Members of the treatment team should not lead the patient to believe or expect that the maxillofacial prosthodontist will be able to completely restore original appearance and function.

Hygiene of the Maxillary Defect

The surgical defect can be rinsed and cleaned following pack removal with the use of a gravity irrigation system (Oral Irrigation Kit, Mentor Corporation, Health Care Products, Santa Barbara, CA) consisting of a holding tank and hose with a plastic nozzle.[171] Powered lavage systems, such as the Waterpik (Teledyne Dental, Buffalo, New York) and the SurgiLav 201 (Stryker Co., Kalamazoo, MI), can also be used and are commercially available for patient use. After the surgical obturator and packing are removed, the patient is instructed to use the irrigation system to rinse three times a day with a saline solution. This solution is made by adding 1 tsp of salt and 1 tsp of sodium bicarbonate to 16 oz of water. The irrigation system must provide enough pressure to ensure that the prepared saline rinse reaches all parts of the surgical defect. Because there are some concerns that the patient may injure the surgical defect and skin graft if a power-spray lavage system is used during the initial healing period of the first 3 weeks, the patient should be instructed in the proper use of the lavage system.

Routine dental hygiene (i.e., tooth brushing and flossing) should be resumed when the surgical pack is removed. Most patients are apprehensive about resuming tooth brushing and flossing owing to concerns that doing so may harm the surgical site, and patients must be specifically instructed to resume oral hygiene. Oral hygiene is one of the most important aspects of postoperative care and cannot be stressed too much.

During the fourth week of postoperative healing, rinsing with a 1:1 dilution of 3% hydrogen peroxide in water can be added to the routine. This mixture is helpful in loosening dried crust and debris in the surgical defect before the patient rinses with the salt and sodium bicarbonate mix. A piece of gauze measuring 4 × 4 inch or a washcloth can be wrapped around the index finger and used to clean the skin graft portion of the defect. A sponge-tipped applicator may also be used for this purpose. After the surgical site has been cleaned, the entire oral cavity, including the tongue, cheek, and remaining hard palate, should be rinsed.

The use of commercial and prescription mouth rinses during the initial healing period is discouraged because the alcohol and phenol in these products may irritate the tissues. These products may also irritate the oral tissues in patients who have received chemotherapy or irradiation as adjunctive treatment.[171,172] The extent of decreased oral opening, loss of innervation, and facial deformity secondary to maxillectomy vary according

to the extent of surgery and adjunctive treatments such as radiation therapy and chemotherapy. When the clinician anticipates these problems, oral opening exercises should be initiated as soon as the patient can tolerate them with regimens previously prescribed in this chapter.

Soft Palate

The soft palate acts as a separator between the oropharynx and the nasopharynx, similar in function to the hard palate. Unlike the hard palate, however, the soft palate moves significantly in function. When the soft palate is involved in the surgical procedure, functionality of the soft palate should be considered. A partial or completely nonfunctional soft palate is difficult or nearly impossible to restore. It is easier to rehabilitate a patient's speech and swallowing if the entire soft palate is removed.[69] Sometimes, however, in cases of limited prosthesis-bearing surface, a thin strip of soft palate can be useful for retention and support of the prosthesis.[64,74]

Primary irradiation of the soft palate may cause palatal incompetency resulting from fibrosis and tumor necrosis. Patients with a radiated soft palate may regurgitate liquid and food through the nose and may have speech impairment.[69] In this situation, prosthetic rehabilitation may be difficult or near impossible because of poor access to the oropharynx.

Mandible

Defects of the mandibular secondary to tumor ablation creates functional and esthetic challenges. Defects of the mandible that are not reconstructed often present with substantial challenges; speech, effective mastication, lip posture, bolus control, and dental malocclusion are common challenges associated with this type of procedure. Most notably, the mandible will deviate to the side of the defect thus compromising occlusion (**Fig. 29.28**). Prosthetic rehabilitation with a mandibular resection prosthesis can often reduce these challenges. As with any prosthesis, retention and stability of the mandibular resection prosthesis can be improved with the remaining mandibular teeth and endosteal implants. A nonmobile soft tissue base is critical to prosthetic success. A flap reconstruction of the mandibular defect has improved the quality of the prosthetic rehabilitation.[45]

Figure 29.28. Patient following segmental mandibular resection, without reconstruction, in maximal intercuspation. Upon opening, the mandible will deviate to the side of the defect (*right*) and dental intercuspation is minimal.

Free-tissue transfer has revolutionized mandibular reconstruction because of its predictability and improved prosthetic outcomes. The most commonly used flap to repair mandibulectomy defects is the fibula free flap. Similar to repair of a maxillary defect, the fibula flap appears to be the most adaptable graft providing adequate bone length and quality to repair any defect of the mandible.[167] The fibular flap is an excellent choice for dental implant placement and support of a prosthesis.

Most patients who have had reconstruction of the mandible can present with an inadequate vestibular depth, and a bulky, load-bearing tissue base over the reconstructed alveolar ridge, making prosthetic rehabilitation difficult or impossible. Often, flap revision surgery, that is, liposuction of the soft tissue component of the flap and placement of dental implants, is necessary for adequate prosthetic rehabilitation[69,74] (**Fig. 29.29**).

Figure 29.29. Fibula flap reconstruction after segmental mandibulotomy followed by postoperative radiation therapy. Note the tongue is tethered by the flap, making prosthetic rehabilitation challenging. Revision of the flap is needed in order to prosthetically rehabilitate this patient to create space for prosthetic teeth; note the indentations from the maxillary teeth on the distal aspect of the flap.

If the normal association of the mandibular segments with the glenoid fossa and maxilla is not maintained, prosthetic rehabilitation may be limited or even impossible. The posterior maxillary teeth, particularly the third molars, opposing the mandibular reconstruction may need to be removed to prevent trauma to soft tissue flaps. When reconstruction is not indicated in a patient who has had a mandibulectomy, removal of the condyle and ramus on the affected side prevents migration of these structures toward the maxilla, thereby facilitating prosthetic rehabilitation.

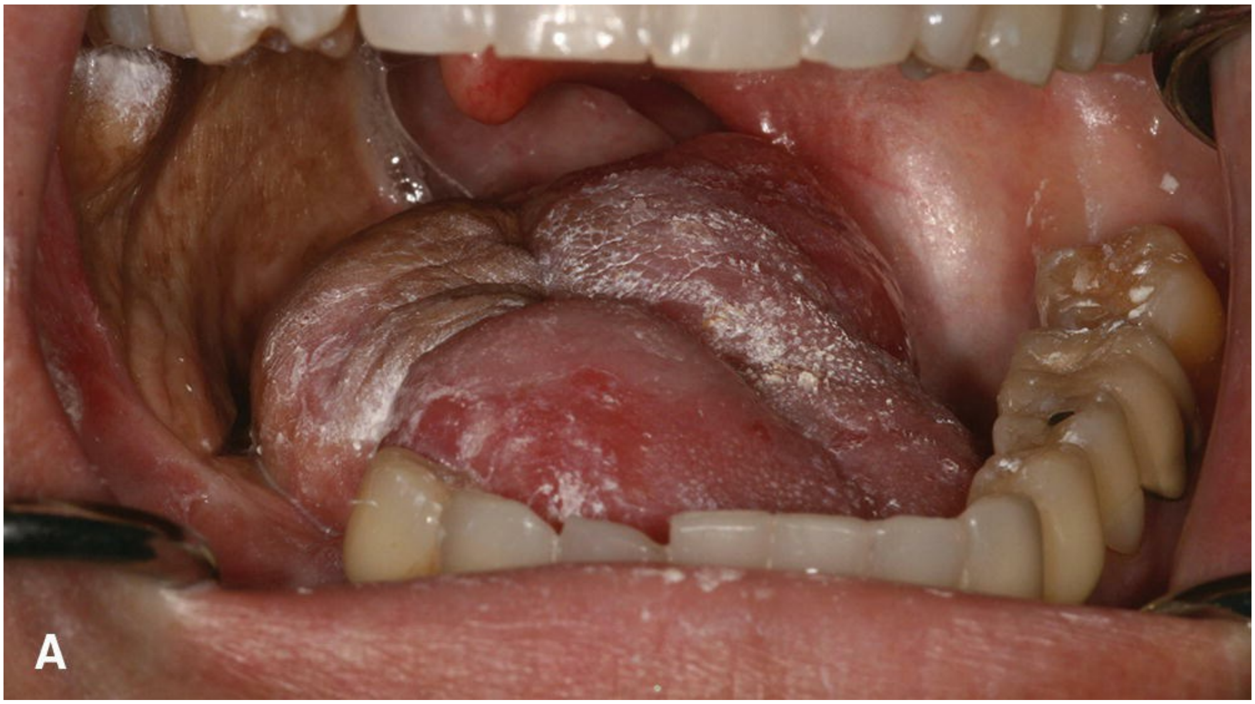
Marginal mandibulectomies (alveolectomies) can be reconstructed primarily with an STSG. Primary closure of these defects, when the tongue/floor of mouth is sutured to the buccal mucosa, often leads to

difficulty with prosthetic rehabilitation because the prosthetic space has been invaded and the tissue is substantially mobile decreasing prosthetic stability (**Fig 29.30**). Skin grafts provide a sound prosthesis-bearing surface and also separate the floor of the mouth from the buccal mucosa.[74] As with the maxilla, conservation of the supporting tissue in the mandible is important when possible.

Figure 29.30. Primary closure of the buccal mucosa, native tongue, and free flap reconstruction. This obliterates the prosthetic space necessary for mandibular resection prosthesis making successful prosthetic reconstruction difficult.

Palatal Augmentation Prosthesis

Speech and swallowing dysfunction are common problems in patients after glossectomy without or with flap reconstruction. Palatal augmentation prostheses modify the contours of the palate to allow for adequate tongue contact during speech and swallowing (**Fig. 29.31**). Articulation is accomplished, in part, by precise positioning of the tongue against the palate, teeth, and other oral structures.[154] Deglutition requires maximal contact of the tongue to the palate. Reduced tongue contact will impair speech and swallowing and recontouring the hard palate with a prosthesis allows for improved lingual contact.[154]



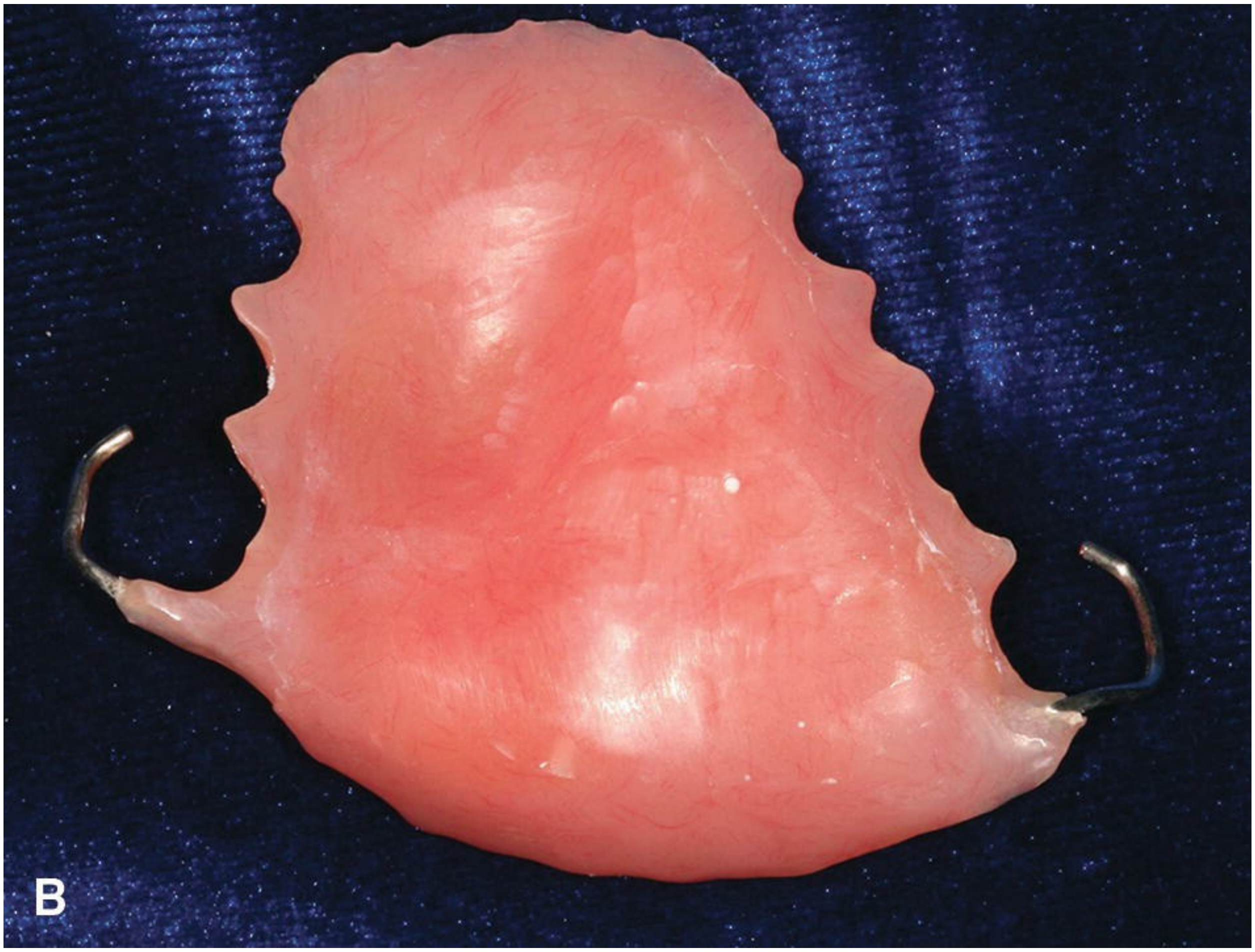


Figure 29.31. A: The limited range of motion of the tongue following partial glossectomy and radiation therapy. **B:** Palatal augmentation prosthesis that allows for appropriate lingual contact maximizing intelligible speech and adequate swallowing.

A direct correlation has been established between the amount of lingual tissue removed and impairment of articulation.[154] Patients who have speech and/or swallowing challenges postoperatively, regardless of flap reconstruction, may benefit from this type of prosthesis. A review of the studies has shown that patients with severe restrictions in tongue–palate contact following resection had an improvement in speech (86%; 36 of 42 subjects) and swallowing (86%; 32 of 37 subjects).[173]

PROSTHETICS FOR FACIAL DEFECTS

Preoperative Evaluation

Traditional facial prostheses include the nasal, orbital, and auricular prostheses. Multidisciplinary care is integral to successful prosthetic rehabilitation and can directly impact timing of prosthesis fabrication, overall cost, and overall success of the prosthetic rehabilitation. This will better prepare the patients not only physically for prosthetic rehabilitation but also psychologically for the changes that they will experience.[67] The preoperative appointment is felt to be a critically important aspect of prosthetic rehabilitation, as this appointment is reserved for setting realistic expectations and explaining risks and benefits of prosthetic rehabilitation and potential complications, which will better prepare the patients for the changes in lifestyle and appearance that they will experience. Comfort, ease of placement/removal, cleansability, and pleasing esthetics are the primary goals of any facial prosthetic rehabilitation.

During the preoperative evaluation, the maxillofacial team should also discuss: the design of the prosthesis, process of fabrication, time frame for fabrication, types of prosthetic materials available, prosthesis longevity, and associated costs. It is imperative to discuss facial and prosthetic hygiene as well as appropriate prosthetic maintenance. The esthetic expectations should be met with an honest discussion of realistic outcomes. Viewing examples of facial defects and prosthetic restoration is often most helpful to patients. Preoperative photographs of the patient can be taken to provide a record of facial features and aid in visualizing the size and contours of the future prosthetic. In some cases, where there is minimal anatomic distortion, a facial moulage (impression) can be made of the affected area before surgical resection. The dental stone cast created from the moulage can be a guide for future prosthetic rehabilitation.

Cases involving osseointegrated craniofacial implants also require preoperative assessment. Factors such as bone quality and volume, soft tissue thickness, and need for radiation therapy may affect the outcomes of craniofacial implant rehabilitation and must be appropriately evaluated prior to surgical intervention.[174–182] Surgical templates, made by the prosthetic team, are recommended to ensure proper placement of the implant(s) in the available bone and to facilitate implant placement.

General Surgical Guidelines and Prosthetic Rehabilitation

Retention is a primary component in the success of any prosthesis, particularly a facial prosthesis.[183] Prostheses can be retained by engaging anatomic undercuts, adhesive, double-sided tape, osseointegrated implants, or a combination of these methods. An appropriate prosthesis-bearing surface is also integral to success of the prosthesis. The ideal postsurgical site characteristics vary depending on type of facial prosthesis. An ablative procedure performed without an understanding of maxillofacial prosthodontic principles may provide a cure but leave the patient orally and esthetically handicapped. Facial defects can be optimized for prosthetic rehabilitation through preoperative discussion between the ablative and reconstruction surgeons and the maxillofacial prosthodontist and consideration of several simple, surgical principles.

These general principles are as follows:

1. Bony margins should be smoothed and rounded to minimize the risk of bony exposure and allow for the comfortable use of prosthesis.
2. Placement of an STSG on exposed bone or periosteum not covered with free tissue or a pedicled flap will resist the abrasive forces of prostheses and decrease mucous secretion in the defect. Prosthesis hygiene and retention are improved by providing an adequate gluing surface.
3. Unsupported tissue tags should be removed, as this tissue is difficult to capture during a moulage procedure. Prostheses fabricated over tissue tags frequently are overcontoured and, due to facial movement, difficult to retain.
4. Donor tissue, ideally, should match the recipient bed adequately and be relatively hairless. Excessive hair growth will interfere with prostheses retention; laser hair removal may be necessary postoperatively.
5. Excessively bulky flaps can obliterate the prosthetic space, making prosthetic rehabilitation difficult or impossible. Revision of the flap may be necessary to provide adequate space for a better outcome.

Postsurgical Evaluation

The patient should return to the maxillofacial prosthetic team postoperatively to evaluate healing and the extent of anatomical loss. At this point, the time frame for fabrication of the prosthesis will be decided. Factors deciding this

time will be dependent on the presence of exposed bone, infection, or bulky soft tissue flaps and the need for adjuvant therapy. These complications will delay prosthetic rehabilitation and should be discussed with the surgeon to discuss possibility of revision. Gentle palpation of the prosthesis-bearing surface can identify areas of tenderness, edema, friable/bleeding tissue, tissue tone, and mobility.[184] Hypermobile tissue can significantly decrease prosthesis retention and thus poses a significant challenge.

Implant position can be evaluated at this point and thus determine the future retentive mechanism. Prosthetic components are varied. Implant-retained facial prostheses are often retained by magnets or, at times, dental components, for example, locator attachments can be used to retain a substructure. If osseointegrated implants are used, 6 months is recommended for adequate osseointegration prior to prosthetic rehabilitation. Prior to prosthetic rehabilitation, the prosthesis-bearing tissue ideally should be dimensionally stable to ensure an accurate fit of the prosthesis.

Biomaterials

The success of any facial prosthesis is dependent on the physical and mechanical properties of the biomaterial used. Since the 1960s, elastomeric material, that is, silicone rubber, has been the most commonly used biomaterial in facial prosthesis fabrication.[185] The ideal mechanical properties of silicone include durability, ease of manipulation, and flexibility similar to that of skin. This material can also be colored to mimic human skin shade and texture relatively easily; coloration of this material can be easily accomplished by either intrinsic or extrinsic coloring with simple oil-based paints and pigments.[186,187] Limitations of silicone rubber include poor edge strength, limited material longevity, discoloration over time, and the ability to support fungal growth; because of these limitations, the average lifespan of the prosthesis is 1 year. Exposure to ultraviolet light, daily application, and removal of adhesive are also thought to decrease longevity.[188,189]

Acrylic resin is often utilized in facial prosthesis, particularly for substructures with samarium cobalt magnets. These substructures help guide the prosthesis into place as well as house the retentive components needed for prostheses for both conventional and implant-retained prostheses. Additionally, acrylic resin is used to fabricate an ocular prosthesis used in an

orbital prosthesis.

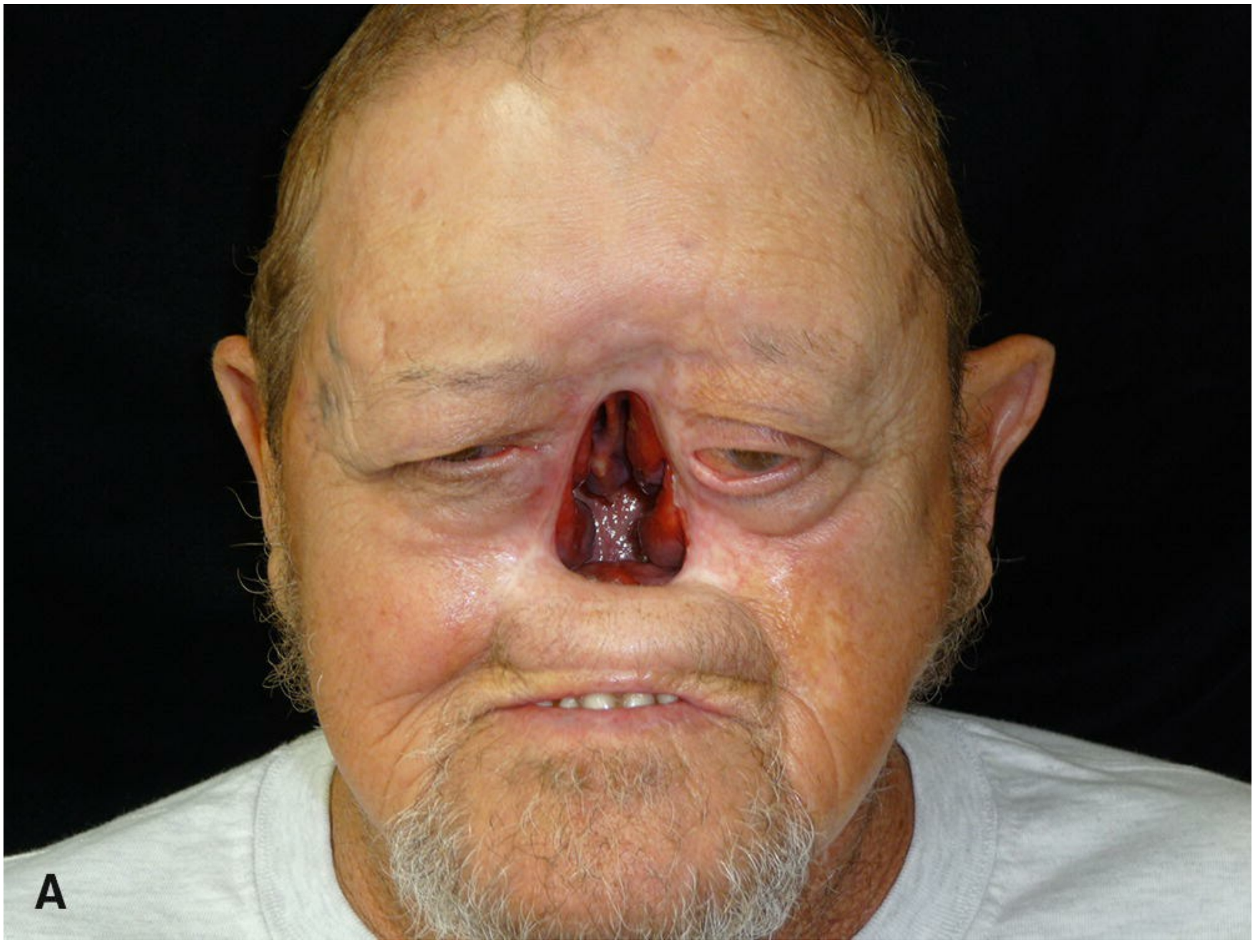
Prosthetic Retention

Multiple retentive mechanisms are available for facial prosthetic rehabilitation. Engagement of anatomic undercuts is useful in retaining a prosthesis, although, depending on location, or tissue friability, these undercuts may not always be available. The type of prosthetic retention is generally directed by the patient's defect site and contour, the quality of the underlying hard and soft tissue, and tissue movement with facial expressions. Medical-grade adhesive and double-sided tape are most often used to retain facial prostheses. Prostheses can be extended to provide adequate gluing surface; however, facial movement is the limiting factor. Adequate adhesion cannot be achieved on friable, weeping, or thin tissue. Adhesive interaction with the skin can affect the longevity of the bond, decreasing prosthesis retention, and lead to dermatologic sensitivity/irritation.[24] Maintenance of the skin and prosthesis requires considerable daily effort and dexterity by the patient. Patient acceptance and confidence with the prosthesis relies upon predictable retention of the prosthesis. Endosteal implants are becoming more common in patients requiring facial prostheses; however, this may not preclude the need for adhesive retention as adhesive may still be required to disguise the margins of the prosthesis.

Nasal Prosthesis

Malignancies involving the nose may require complete or partial rhinectomy. When nasal bones and the anterior nasal spine are preserved, local flaps produce excellent results. However, if these structures cannot be preserved, a prosthesis is often the most esthetic option. Saving even a portion of the nasal bone allows vertical support for the prosthesis and, if necessary, for eyeglasses. Reducing the profile of the distal end of the nasal bone allows for a prosthesis to be overlaid without increasing nasal projection. This procedure also gives the clinician greater control in determining the final dimensions of the nasal prosthesis, which may need to be decreased to avoid unfavorable alteration of lip contours following rhinectomy. Unsupported tissue tags, such as an alar remnant, should be resected.[190,191] The borders of the resection and any exposed bone, such as the nasal bone or the anterior nasal spine, should be lined with an STSG to provide prosthetic support for

the prosthesis as well as help reduce secretions (**Fig. 29.32**).[190] If the septum is preserved, the anterior border should be reduced to increase the space for a properly contoured prosthesis. Contracture of the graft at the periphery of the surgical site decreases the amount of muscular action during facial movements (e.g., smiling and eating) and makes the prosthesis more stable.



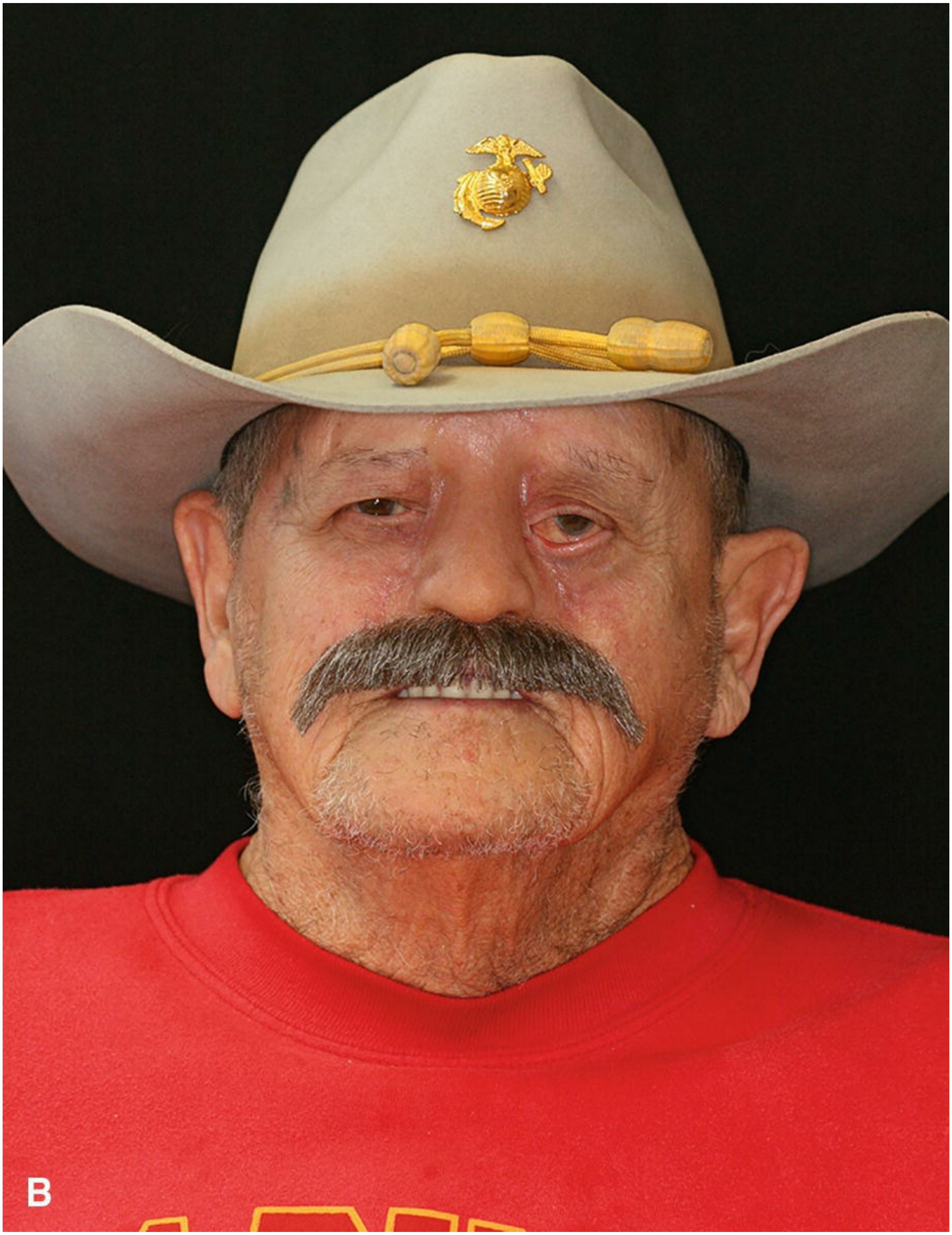


Figure 29.32. A: The skin graft on the superior aspect of the defect enhances adhesion of the liquid water-based adhesive used to retain the nasal

prosthesis. **B:** Moustache masks superiorly placed lip.

Following a rhinectomy procedure, the upper lip tends to contract superiorly despite the surgeon's efforts to maintain a normal intraoperative position, and therefore, every attempt should be made to maintain normal lip position.[191] When this contraction occurs, the lip is everted and raised to expose the anterior dentition. With preservation of the nasal spine, however, the superior lip attachments remain in its normal position (**Fig. 29.33**).

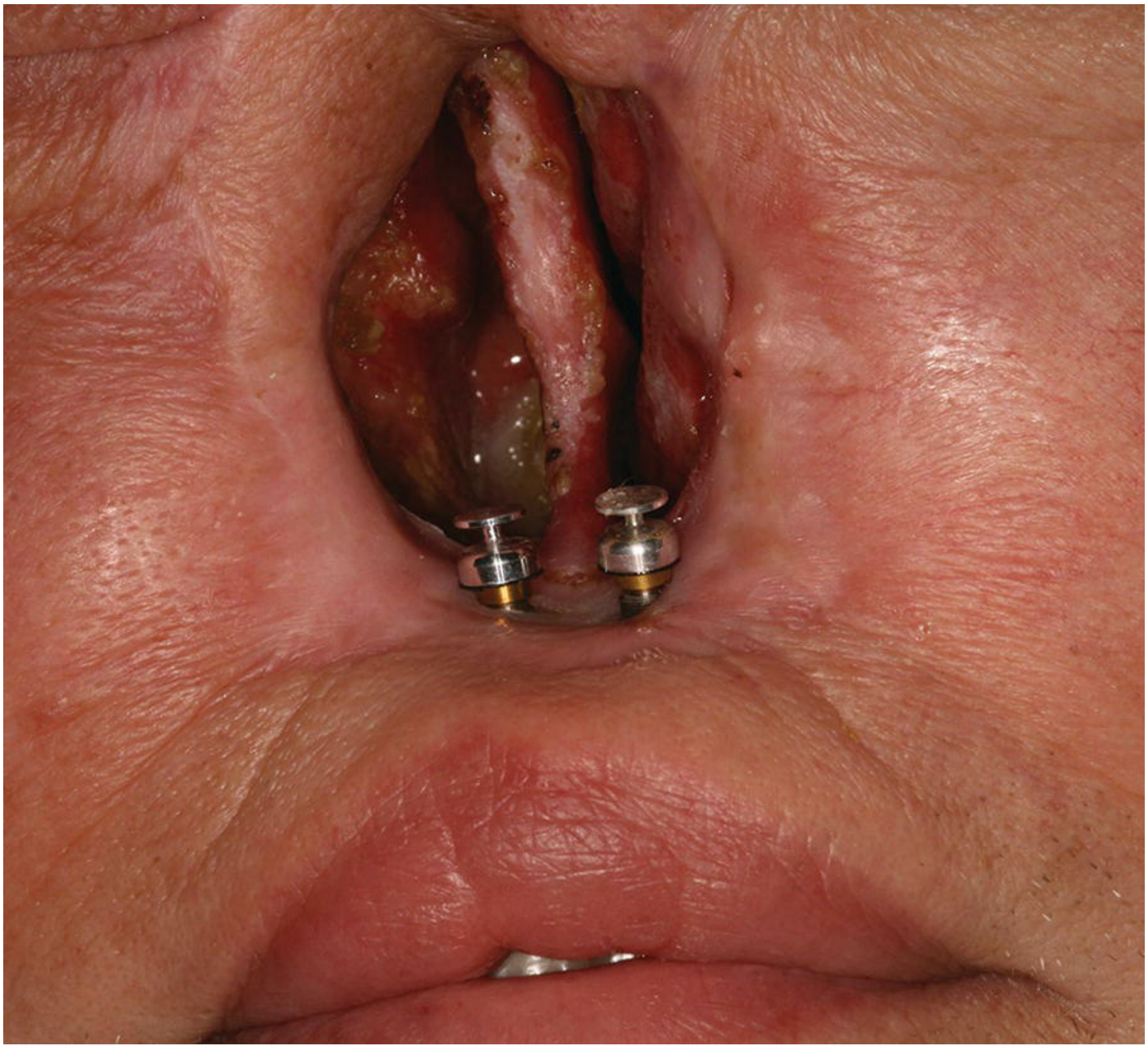
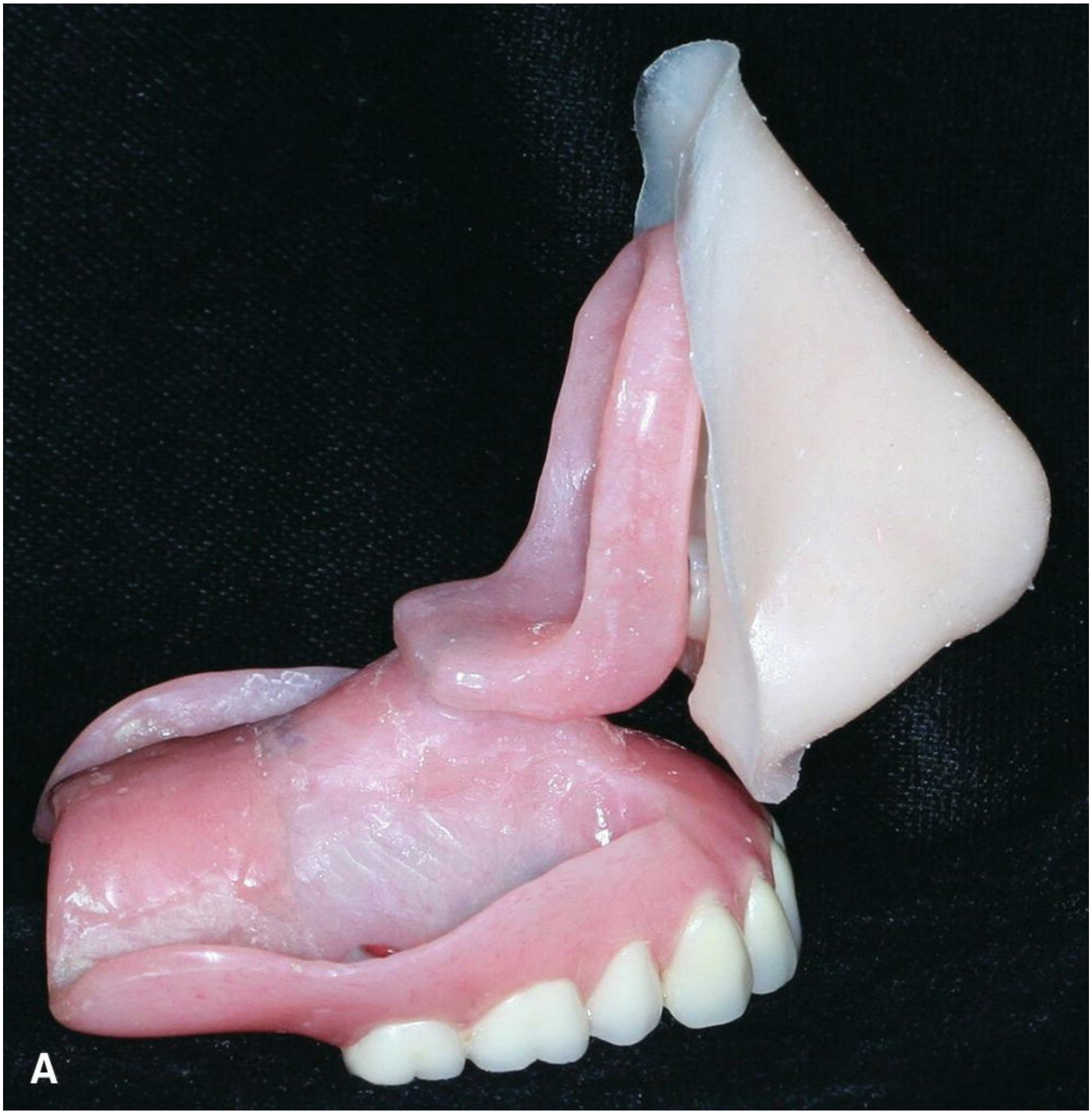


Figure 29.33. Patient following rhinectomy for SCC of the nasal cavity. Notice the upper lip has everted superiorly. Implants were used with locator attachments in order to retain a facial prosthesis.

Combined Defects

In cases when a nasal defect extends into the oral cavity, a stable intraoral prosthesis can increase retention of a facial prosthesis. This is achieved by extending the oral prosthesis into an anatomic recess within the midface defect, mechanically connecting the intraoral to the facial prostheses (**Fig. 29.34**). Most commonly, magnets serve as an attachment.[192,193] A large defect of the midface can be reconstructed by microvascular free flap, effectively closing the sinus cavity; however, if a patient desires a prosthesis after this type of reconstruction, the flap should be positioned to allow adequate space for development of proper contours of the prosthesis. Concave flap contours generally produce a better esthetic result.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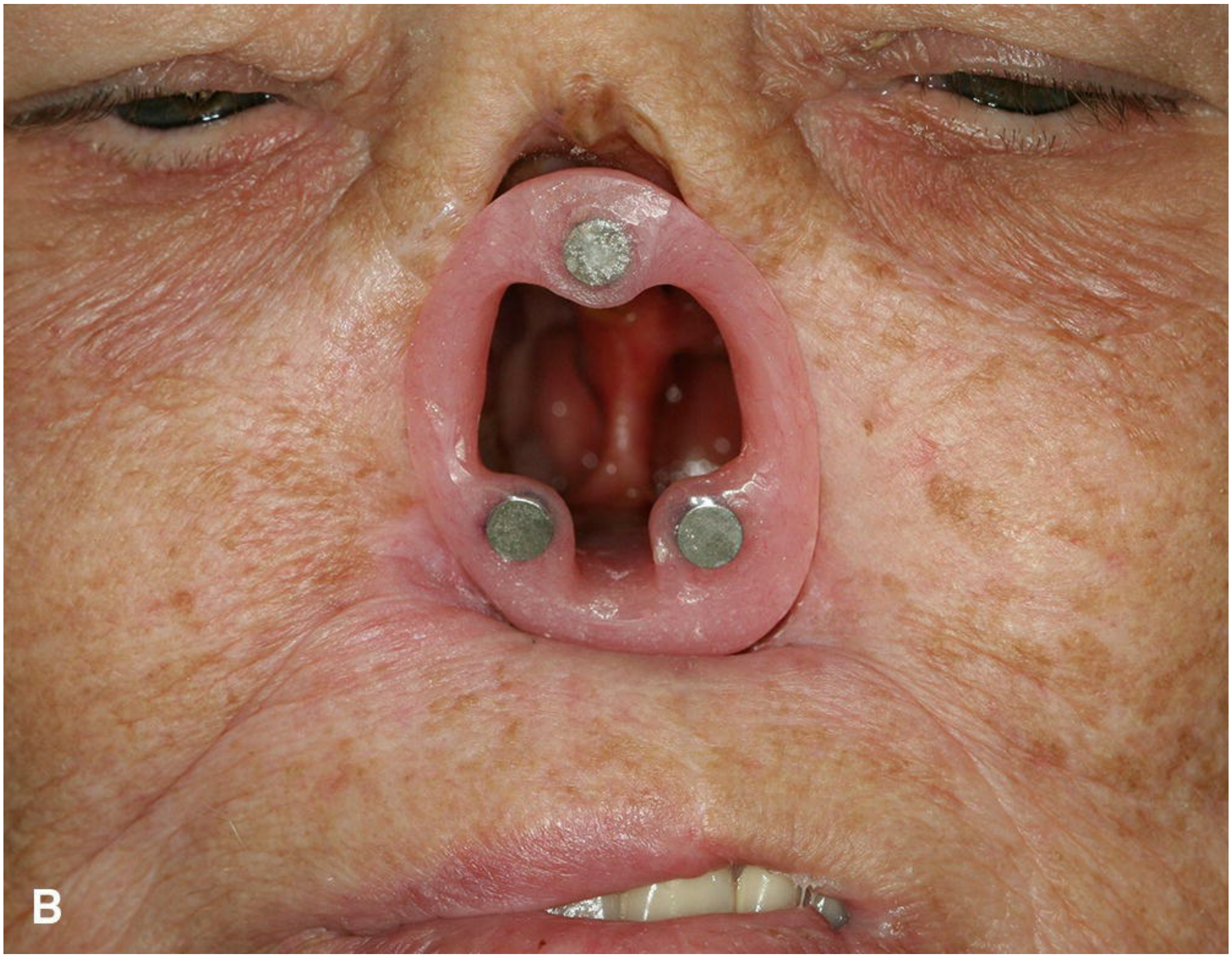
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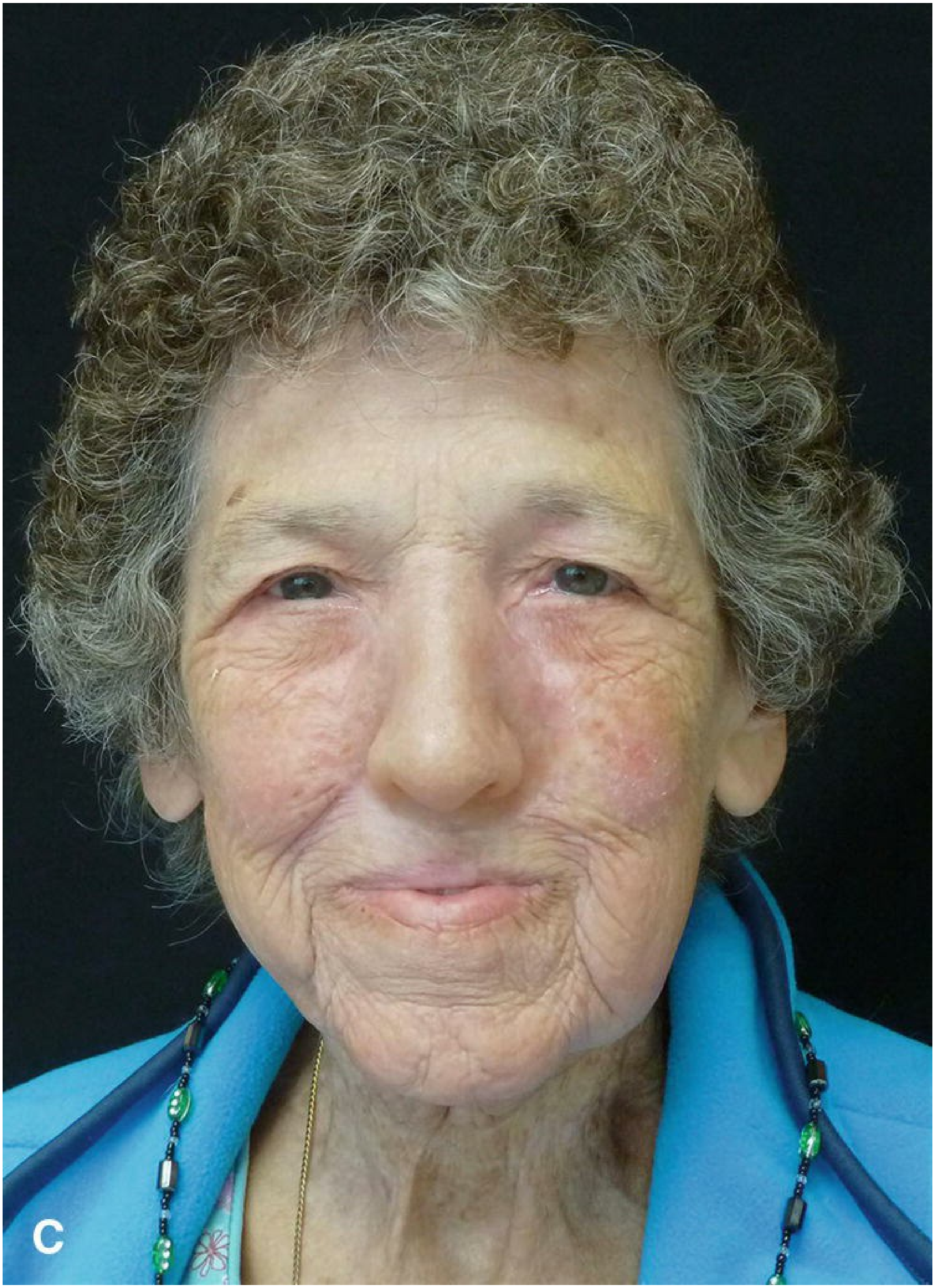

C

Figure 29.34. A: Nasal prosthesis prior to extrinsic coloring. Note that maxillary obturator is connected to the acrylic substructure for the nasal prosthesis. **B:** Acrylic substructure in place. **C:** Final prosthesis in place.

Orbital Prosthesis

The design and fabrication of an orbital prosthesis following an exenteration is thought to be one of the most esthetically challenging restorations. The difficulty lies in the fact that the prosthesis must mirror image the existing eye and its unique contours of the eyelids and surrounding tissues exactly. Minor inconsistencies are easily noticeable to the casual observer. The perfect recipient site is needed to achieve an esthetically acceptable orbital prosthesis.

The eyelids should be resected while the position of the eyebrow is maintained. An STSG is placed to the depth of the defect, covering any exposed bone allowing for adequate hygiene (**Fig. 29.35**). This STSG also allows the prosthesis to be extended into the defect for greater orientation and stability.[194] Occluding the orbit with bulky flaps should be avoided (**Fig. 29.36**). A concave bony orbit lined with an STSG is the ideal recipient site for an orbital prosthesis, providing an immobile tissue foundation, the depth required for mirror imaging, and a good adhesive platform.


A

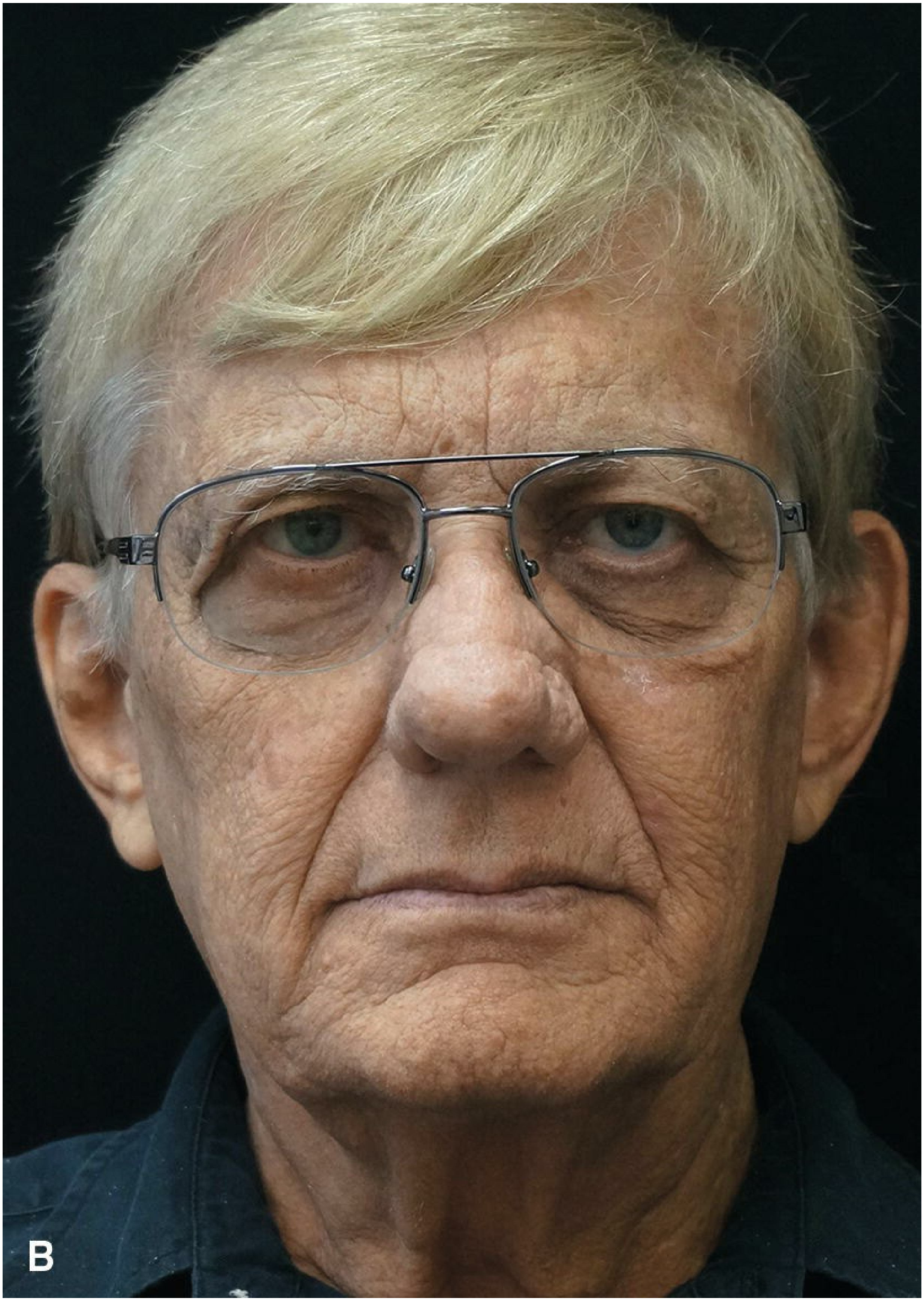

B

Figure 29.35. A and B: The patient is a 63-year-old male with a history of recurrent squamous cell carcinoma of the right bulbar conjunctiva, caruncle, and lower palpebral conjunctiva who underwent a right orbital exenteration. The concavity of his defect provides ample space for an ocular prosthesis to be correctly positioned within the orbital prosthesis resulting in excellent esthetic results. Eyeglasses aid in disguising the borders of the prosthesis.

Figure 29.36. Prosthetic restoration of an orbital defect is one of the most difficult defects to restore. Bulky flaps that occlude the orbit make restoration difficult. Note the flap invades the space for ocular prosthesis. A concavity defect lined with an STSG is preferable whenever possible.

Auricular Prosthesis

As with the nose, surgery of the ear can vary from subtotal resection to a total auriculectomy. With a total auricular prosthesis, the clinician has more freedom to determine the shape, size, and location of the prosthesis, allowing for easier fabrication than a partial auricular prosthesis. Unlike the orbital prosthesis, direct comparison of the natural ear to the prosthetic ear is almost impossible. The recipient area should be flat or concave; convexities from excessive tissue bulk can hamper esthetic results; however, tissue concavities assist in the orientation and stability of the prosthesis and allow the margins to extend in a 0-degree emergence profile.[174]

The tragus is a stabile prosthetic landmark and, therefore, should be preserved whenever possible.[194] The tragus allows the anterior margin of the prosthesis to be hidden behind the posterior flexure and facilitate prosthetic placement. The inferior half of the soft tissue pinna is of little or no value. The lobe of the auricle lacks cartilaginous support and therefore is normally drawn down and away from the head, also of little value prosthetically. The lobe is difficult to capture in an impression, and bilateral symmetry usually cannot be achieved. The superior half of the auricle has better cartilaginous support but tends to distort postsurgically. Preserving a portion of the root of the helix provides a good landmark and support for eyeglasses. This area may help later in vertical support of the prosthesis. The anterior superior helical rim should remain if possible. Posterior regions may be grafted (**Fig. 29.37**).


A

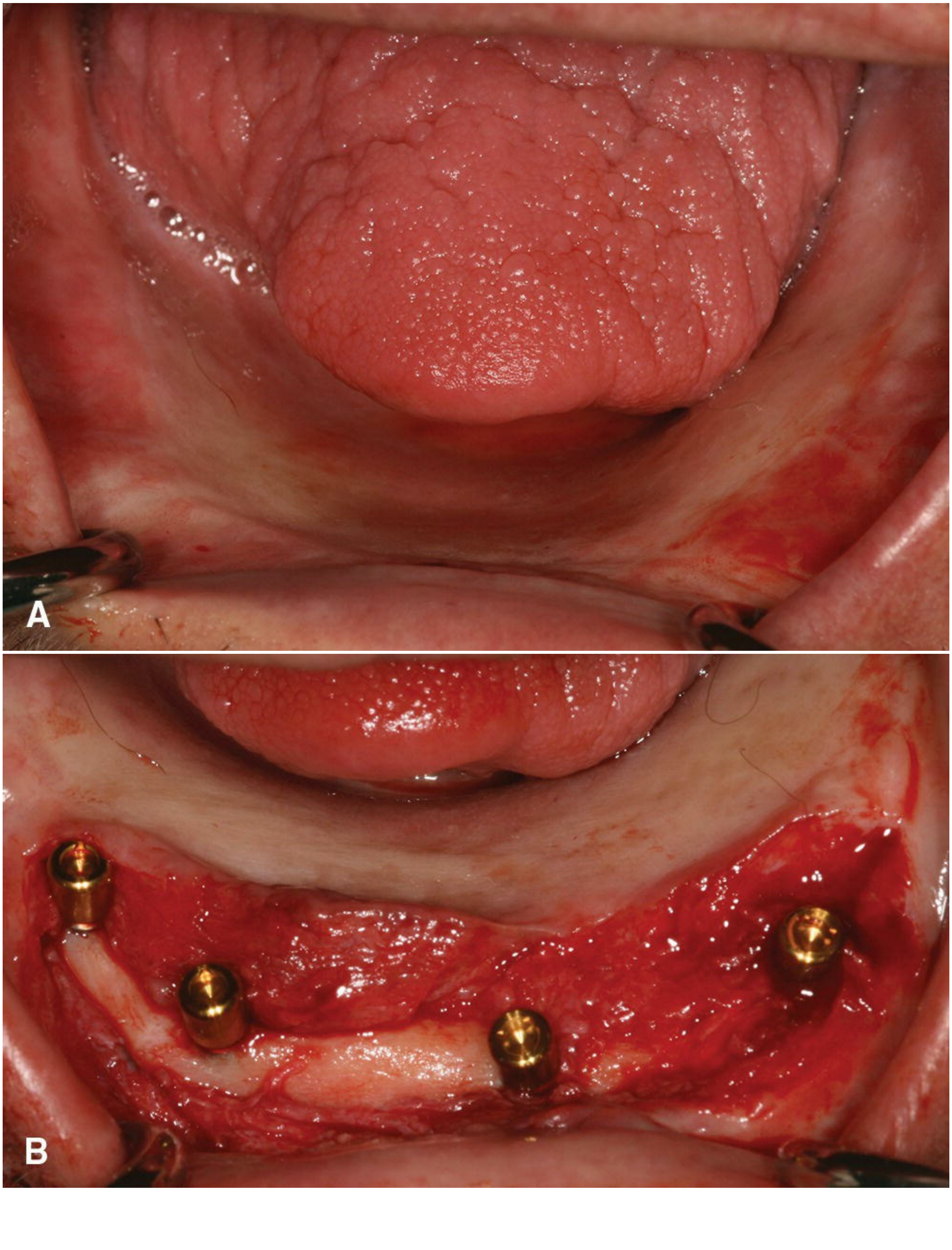
Figure 29.37. A: Patient is with a history of recurrent squamous cell and basal cell carcinoma of the right external auditory canal. The flat contour of the skin paddle of a microvascular flap absent of a stable anatomical

landmark (such as the tragus) is a challenge for repeatable correct positioning of the auricular prosthesis. Retention of the prosthesis achieved with the use of a medical-grade double-sided tape. **B:** Final prosthesis.

Prosthetic replacement of missing facial tissues has several advantages over surgical reconstruction. The process allows for periodic evaluation and cleaning of the surgical site and is an alternative to surgery in unsuitable candidates. The fabrication process is relatively short, and the dental clinician has complete control of the color, shape, and position of the prosthesis. Disadvantages of prosthetic rehabilitation include possible irritation of the tissue site, the need for periodic remakes, and the need to rely on some form of retention. Furthermore, the patient may view the prosthesis as a mask and not as part of his or her body.

OSSEOINTEGRATED IMPLANTS

A variety of implant systems are available, and each has its own characteristics. Most of these systems have similar placement and restoration procedures that are usually done in two stages. Stage 1 is the surgical placement of the implant in the recipient bone. The surgical sites are prepared in bone by techniques designed to prevent soft and hard tissue damage at the cellular level.[68] Initially, the soft tissue is reflected to expose the bone. The recipient site of the bone may need to be flattened to provide proper surface adaptation of the implant. An air-driven, slow-speed handpiece (15 to 20 rpm) with copious amounts of irrigation is then used in preparing the recipient site and preventing overheating of the bone.[68] Implant sites are enlarged in small increments with the use of increasingly larger burrs and are then tapped to receive the threaded implants. Following placement of the implant, a cover screw is placed, and the surgical site is readapted by primary closure of the tissue flap. The implants are not disturbed for 3 to 4 months to allow for osseointegration, especially for implants placed into a fibula (**Fig. 29.38**). Following this period, stage 2 can be initiated. The implants are uncovered and the abutments placed. An abutment is positioned onto the implant and secured in place to allow for interlocking attachments that will connect and support an overlying prosthesis.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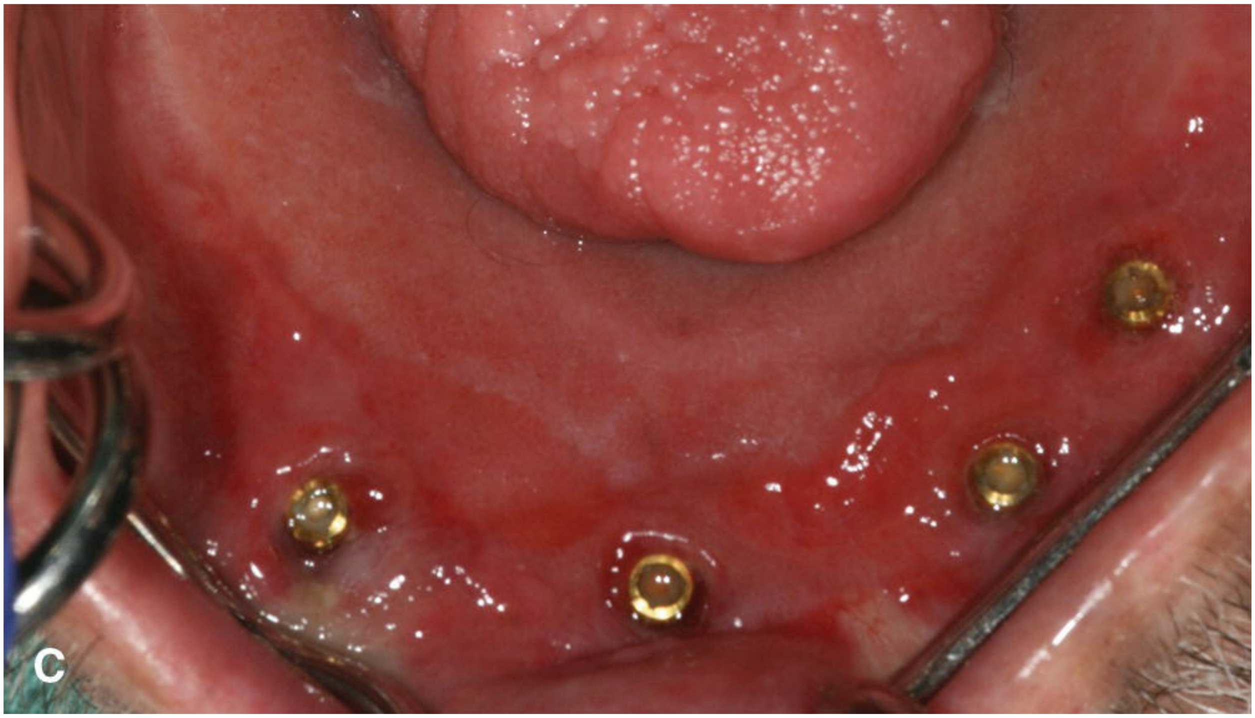

Figure 29.38. A: Mandibular reconstruction using a fibular free flap. With the flat architecture of the reconstructed mandible, a conventional prosthesis without implants is difficult to retain. **B:** Implants into a fibula following stage II (uncovery). **C:**Final healing; tissue ready for fabrication of the prosthesis.

Immediate loading of implants, when the prosthetic abutment is placed at the time of the implant placement, is a common practice. Multiple publications have discussed immediate loading. The authors concluded that immediate loading is successful in select patients, although there is increased risk of failure associated with immediate loading versus conventional loading.[192,194,195] A survey of prosthodontists revealed that just over half of the surveyed prosthodontists (61%) use immediate loading in their practices.[193] Despite positive, high-level research, immediate loading remains a somewhat controversial practice in dentistry, given that 39% report not using this technique. The most commonly cited reason, according to this study, was that they don't believe the loading philosophy.[193]

PROSTHETIC REHABILITATION AFTER RADIATION THERAPY FOR

HEAD AND NECK CANCER

The primary concern of the prosthodontist in fabricating a prosthesis for a patient who has been treated with radiation of the head and neck is the risk of traumatizing extremely friable tissue. In addition to adhering rigidly to proven prosthodontic principles, the prosthodontist must exercise special caution in designing the prosthesis to avoid causing trauma to tissues previously subjected to surgery and/or radiation. For example, the portions of an obturator that are adjacent to surgical margins should be fabricated of acrylic resin to permit easy adjustment. Tooth gingival margins should be avoided, and all surfaces in contact with tissue must be thoroughly polished to minimize the exposure of these tissues to plaque buildup on the prosthesis.

Radiation therapy permanently impairs the healing capability of the treated tissue volume. For this reason, prosthodontic rehabilitation of previously radiated patients requires radiation treatment details.[150,196–198] The geometry of the treatment volume, energy source, total dose, and daily fraction are the most desirable details. In some instances, this information may not be available directly from the treating radiation oncologist; however, careful examination of the patient, together with information the patient can provide, usually suffices for the experienced maxillofacial prosthodontist. Certain characteristics are evident in patients who have previously received therapeutic radiation; for example, the skin within the treatment area is often permanently hyperpigmented, epilation is particularly noticeable in men, and the skin texture is often significantly altered. Telangiectatic changes are common in previously radiated skin and mucosa. If major salivary gland tissue was within the radiated tissue volume, xerostomia is often very apparent.

Prosthodontic rehabilitation for patients who have received radiation therapy requires that the restorative dentist pay particular attention to detail. Radiated tissues do not necessarily become less sensitive with time and can readily change in contour. Therefore, a regular recall schedule is highly recommended for evaluation and possible adjustment of the prosthesis or modification in previously radiated patients.

A problem frequently encountered after maxillectomy by a patient who has had postsurgical radiation therapy is a definite decrease in interocclusal distance or trismus. Instituting a physical therapy program designed to

overcome surgically induced fibrosis in the immediate postsurgical period can help to prevent this reduction of the oral opening. Because surgically traumatized muscle fibers are extremely susceptible to radiation-induced fibrosis, a near-normal intermaxillary opening may not be attainable unless it is achieved by the time radiation therapy begins. Radiation also produces changes in the capillaries and arterioles, thereby further reducing an already surgically reduced blood supply to the muscles of mastication. Failure to treat this problem after radiation therapy results in continuing progressive muscle fibrosis and a further decrease in oral opening.

CONCLUSION

The oral cavity should be thoroughly evaluated in all patients diagnosed with head and neck cancer. Preventing and treating the oral complications of cancer and its therapy are important responsibilities of the dental oncologist or maxillofacial prosthodontist, and anticipating primary and secondary mucosal insults and recognizing oral complications promptly in this setting can decrease the incidence of such complications or ameliorate their morbid adverse effects. By fostering communication and compliance among the multidisciplinary team, the prosthodontist can ensure the quality of preventive and prosthetic treatment, as well as maintenance care, for patients with cancer of the head and neck.

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30 General Principles of Radiation Therapy for Cancer of the Head and Neck

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Treatment of cancer of the head and neck continues to evolve through our improved understanding of head and neck cancer biology and risk factors, as well as the emergence of promising new treatment approaches. More than ever before, the close collaboration of the head and neck surgeon, radiation oncologist, and medical oncologist (in addition to ancillary experts) is critical to optimize outcome for patients with cancer of the head and neck. Our expanding knowledge of human papillomavirus (HPV)-associated cancer of the head and neck along with steadily improving surgical, radiation, and chemotherapy techniques is affording new opportunities to increase tumor control rates and diminish normal tissue toxicities. Maintaining a modern and balanced perspective regarding the respective strengths and weaknesses of each treatment modality enables each practitioner to advocate most effectively for head and neck cancer patients. The primary purpose of this chapter is to provide a broad overview of “radiation for head and neck cancer” in an effort to strengthen the practitioner’s knowledge base on behalf of the patients that they serve who have cancer of the head and neck.

In this chapter, we provide an overview of head and neck radiation oncology. We start by reviewing important clinical trials that have shaped the management of patients with cancer of the head and neck and describe several recent advances that are likely have significant impact in the years to come. We then provide an overview of typical radiation workflow from pretreatment assessment through posttreatment follow-up. We provide several simple definitions to clarify modern approaches in radiation

oncology. We provide a brief overview of radiation physics and radiation biology with the goal of helping the reader understand important contributions of these fields to the care of the head and neck cancer patient. Finally, we offer comments addressing the importance of multidisciplinary care for patients with cancer of the head and neck.

Key Studies Impacting Radiation Oncology Practice

The role of radiation therapy in cancer of the head and neck first emerged in the early 1900s with single fraction, and thereafter, multifraction treatment schedules developed in Europe (for detailed discussion, see Thames and Hendry's *Fractionation in Radiation*[1]). The field advanced to incorporate radiation in the postoperative setting in the 1950s [Fletcher and colleagues at MD Anderson Cancer Center (MDACC)] with further expansion to the definitive setting by Million and colleagues (University of Florida) and Wang (Harvard) in the 1960s to 1980s. Over the past 25 years, there have been a series of landmark clinical trials (Table 30.1) that have influenced the practice of radiation oncology in treating patients with cancer of the head and neck. Several but not all of these studies are briefly discussed here.

Table 30.1 Sampling of Trials with Impact on Current or Future Head and Neck Radiation Oncology Practice

Landmark Trial	Treatment Arms	Summary of Results	Impact
VA Larynx Trial[2]	Phase 3 randomized control trial comparing neoadjuvant chemotherapy + radiation vs. surgery and postoperative radiation in squamous cell carcinoma of the larynx	2-year survival was 68% in each arm with 64% of patients in the chemoradiotherapy arm maintaining larynx preservation at early follow-up	Established chemoradiotherapy as an organ-preserving option for patients with cancer of the larynx
EORTC HPX Trial[3]	Phase 3 randomized control trial comparing neoadjuvant chemotherapy + radiation vs. surgery and postoperative radiation in squamous cell carcinoma of the larynx and hypopharynx	3-year survival was 43% in surgical arm and 57% in chemoradiotherapy arm	Established chemoradiotherapy as an organ-preserving option for larynx and hypopharynx cancer patients
RTOG 91–11[4,5]	Phase 3 randomized control trial comparing (1) neoadjuvant chemotherapy and radiation, (2) concurrent chemotherapy and radiation, or (3) radiation alone	Survival was similar across all three arms, but laryngeal preservation was highest for the concurrent arm (88%), neoadjuvant (74%), and radiation alone (70%)	Established concurrent chemotherapy as a nonoperative standard of care with radiation
MACH Meta-analysis[12]	Meta-analysis of 15 trials (6,515 patients) evaluating altered fractionation vs. conventional fractionation (no chemotherapy)	Altered fractionation improved survival (3.4% at 5 years) and local–regional control (6.4% at 5 years)	Established that with radiation alone regimens, altered fractionation is better than conventional fractionation
RTOG 0129[29]	Phase 3 randomized control trial comparing altered fractionation + chemotherapy vs. conventional fractionation + chemotherapy. Post hoc analysis of HPV as prognostic factor	Arms were equivalent. 3-year overall survival was 82% in the HPV-positive vs. 57% in the HPV-negative patients. OPSCC patients can be categorized into low-, intermediate-, and high-risk groups	Altered fractionation can be used with concurrent chemotherapy. Treatment of OPSCC patients will be tailored according to risk group
GORTEC 99–02[118]	Phase 3 randomized control trial of (1) standard fractionation and chemotherapy, (2) hyperfractionation and chemotherapy, and (3) hyperfractionation alone	Two chemotherapy arms had similar and significantly better outcomes compared to radiotherapy alone. Acute toxicity was worse in the two hyperfractionated arms	Altered fractionation should be used with caution with concurrent chemotherapy. Altered fractionated radiotherapy alone showed inferior outcomes
MACH-NC8[13,14]	Meta-analysis of 87 trials (16,485 patients) that evaluated the efficacy of definitive chemoradiotherapy	The addition of chemotherapy to radiation improved survival by 4%–5%. Concurrent chemotherapy had the greatest impact on survival. Neoadjuvant and adjuvant chemotherapy did not significantly affect survival	Established that concurrent chemotherapy can be given with radiotherapy for the definitive treatment of stage III–IV head and neck squamous cell cancer
EORTC 22931 and RTOG 9501[17–19]	2 phase 3 randomized control trials of postoperative radiation vs. postoperative radiation + chemotherapy	The addition of chemotherapy improved local–regional control and survival in patients with + margins or extranodal extension	Established that chemotherapy can be given with radiotherapy after surgery in patients with high-risk pathologic features
Bonner et al.[26,27]	Phase III randomized control trial of radiation vs. radiation + cetuximab. First of its kind study in head and neck cancer, allowing for the evaluation of molecular targeted therapy in combination with radiation	The addition of cetuximab to radiation resulted in an absolute improvement in survival of 10% without increased toxicities (except acneiform rash)	Study was the first of its kind in head and neck cancer, allowing for evaluation of molecular targeted therapy in combination with radiation
RTOG 1016	Phase III randomized control trial of radiation + cisplatinum vs. radiation + cetuximab in HPV-associated OPSCC, closed to accrual	Primary end point is noninferiority and less toxicity in the radiation + cetuximab arm	If the radiation + cetuximab arm is noninferior and less toxic, this regimen would offer a deintensified option for patients with HPV-associated OPSCC
ECOG 3311	Ongoing phase 2b randomized study of transoral surgery followed by observation (low risk), chemoradiotherapy (high risk), or randomization to 50 Gy vs. 60 Gy (intermediate risk) in HPV-positive OPSCC	Primary end point is 2-year PFS. Secondary end point is 2-year functional outcome	Study opened in 2014

Curative Role for Radiotherapy

Historically, surgery was the primary treatment of choice for cancer of the head and neck, whereas radiotherapy was reserved for the postoperative setting. In the 1960s to 1980s, several institutions (University of Florida, Harvard, MDACC, among them) advanced a nonsurgical treatment approach by treating selected larynx, hypopharynx, and oropharynx patients with definitive radiotherapy. In the early 1980s, the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group conducted a prospective randomized clinical trial (the VA Larynx trial published in 1991) evaluating whether nonoperative therapy (induction chemotherapy and radiotherapy) could provide equivalent survival compared to surgery and postoperative radiation in local–regionally advanced squamous cell carcinoma of the larynx.[2] The 2-year survival was 68% in each arm with 64% of patients in the chemoradiotherapy arm preserving their larynx in early follow-up. In parallel, the European Organization for Research and Treatment of Cancer (EORTC) conducted a similar study in patients with advanced cancer of the larynx and hypopharynx and observed similar results.[3] The Radiation Therapy Oncology Group (RTOG) and Intergroup performed a follow-up study (RTOG 91–11) for which patients with local–regionally advanced cancer of the larynx were randomized to (1) induction chemotherapy and radiation, (2) concurrent chemotherapy and radiation, or (3) radiation alone. Overall survival was the same across all three arms, but preservation of the larynx was highest in the concurrent chemoradiotherapy treatment arm (88% vs. 74% and 70%).[4] The 10-year update showed similar results.[5] These important studies helped to establish the role of radiation as a curative option in appropriately selected patients with cancer of the larynx and hypopharynx.

Altered Fractionation

The most commonly used fractionation schedule in the United States for head and neck cancer is 1.8 to 2 Gy per fraction given once a day for 35 to 39 treatments 5 days a week for 7 to 8 weeks. Altered fractionation schedules were developed to compensate for rapid and accelerated repopulation (see section “Basic Radiation Biology” below) observed in head and neck squamous cell carcinoma. Clinically, this phenomenon manifests as reduced

local/regional control in patients who have treatment delays extending their overall radiation treatment time[6]–[9] or who have a prolonged interval between surgery and beginning their treatments. Intensifying the radiation dose delivery by treating "faster" is a method to compensate for accelerated tumor cell repopulation.

Several clinical trials have been conducted to evaluate whether intensification of the radiation dose with altered fractionation schedules could improve local–regional control and survival in patients with cancer of the head and neck. Numerous altered fractionation schemes have been used. Hyperfractionation refers to the delivery of multiple smaller fractions per day, whereas accelerated fractionation commonly delivers more than 10 Gy per week. Both hyperfractionation and accelerated fractionation can result in the completion of radiation in <7 weeks but deliver the same (or slightly higher) total dose as standard fractionation schedules. As examples, twice daily radiation (1.15 Gy per fraction × 70 fractions = 80.5 Gy) was compared to once daily radiation (2 Gy per fraction × 35 fractions = 70 Gy) for patients with cancer of the oropharynx by the EORTC. In this randomized trial, hyperfractionation improved local control with a strong trend toward improved survival and no difference in late effects.[10] The Danish group has studied accelerated fractionation in over 1,000 patients randomized to 5 fractions per week (66 to 68 Gy in 33 to 34 fractions) versus 6 fractions per week (same total dose), with the 6th fraction given either on the weekend or as a second daily fraction during one of the weekdays. Local control at 5 years was improved by 10% (70% vs. 60%) for patients treated with 6 fractions per week.[11] Again, no difference in overall survival was seen. The published meta-analysis of these clinical studies showed that altered fractionation regimens delivered without chemotherapy significantly improved local–regional control (6.4% at 5 years) and survival (3.4% at 5 years).[12]

Definitive Chemoradiotherapy

The addition of chemotherapy to radiation has been studied in many clinical trials since the 1970s. Chemotherapy may be given before (neoadjuvant), during (concomitant), and after (adjuvant) radiation or a combination thereof. Pignon et al. conducted a meta-analysis of 87 randomized trials and 16,485 patients (stage III to IV with no prior treatment for cancer of the head and

neck) that evaluated the efficacy of chemoradiotherapy (*m*eta-*a*nalysis of *c*hemotherapy in *h*ead and *n*eck *c*ancer or MACH-NC).[13,14] The addition of chemotherapy conferred a 5-year, 4.5% absolute survival benefit (HR 0.88, 95% CI 0.85 to 0.92). Concurrent chemotherapy was observed to have the most pronounced benefit for survival: 5 years, 6.5% absolute benefit (HR 0.81, 95% CI 0.78 to 0.86) versus 2.4% for neoadjuvant (HR 0.96, 95% CI 0.90 to 1.02) and −1% for adjuvant (HR 1.06, 95% CI 0.95 to 1.18) delivery of chemotherapy.[13] The MACH-NC analysis solidified the addition of chemotherapy (most commonly cisplatin) to radiation as a standard of care approach for the definitive treatment of stage III to IV squamous cell carcinoma of the head and neck, with the preferred sequence being concomitant administration of drug with radiation. It should be noted that this added efficacy is accompanied by increased acute toxicity and possibly some late toxicities including fibrosis and dysphagia although several groups have suggested that these late toxicities are more closely related to radiation dose to critical structures than to the use of concurrent chemotherapy.[15,16]

Postoperative Chemoradiotherapy

Historically, the standard of care for advanced cancer of the head and neck was surgery followed by radiotherapy. For high-risk patients, this still resulted in less than desirable survival outcomes. With the observation that adding chemotherapy to radiation could improve outcome in the definitive setting, the RTOG and EORTC conducted randomized studies that evaluated the addition of concurrent cisplatin chemotherapy to radiation in the high-risk postoperative setting.[17–19] The eligibility criteria differed slightly for both studies and the EORTC study showed a survival benefit to postoperative chemoradiotherapy,[18] whereas the RTOG study showed a marginal benefit.[19] In both studies, positive margins and extranodal extension were common eligibility criteria. A combined analysis of both studies showed that patients with positive margins and/or extranodal extension had improvement in local control, disease-free survival, and overall survival with the addition of cisplatin to postoperative radiotherapy.[17] Patients with other pathologic risk factors (i.e., perineural invasion, ≥ 2 positive nodes, lymphovascular space invasion) did not show a clear outcome benefit from the addition of chemotherapy. These studies established a favored recommendation (in patients deemed fit to receive cisplatin) for the use of concurrent

chemotherapy with radiation in the postoperative setting for those patients with high-risk pathologic features including positive margins and/or ECS.

Recent Advances in Head and Neck Cancer

Over the last 15 years, several new developments promise to advance the evaluation and management of head and neck cancer patients. We discuss several of these that are having an important impact on the care of patients with cancer of the head and neck.

Targeting the Epidermal Growth Factor Receptor

High-level epidermal growth factor receptor (EGFR) expression is reported to occur in ~90% squamous cell cancers of the head and neck and is correlated with reduced survival outcomes and response to radiotherapy.[20–22] Preclinical studies indicate that molecular inhibition of EGFR can enhance radiosensitivity (see below) and that the combination of EGFR inhibition with radiation is synergistic.[23–25]

A phase III trial testing the role of the EGFR inhibitor cetuximab in combination with radiation (compared to radiation alone) was initiated in 1999. Enrolling patients with locally advanced cancer of the head and neck, this study demonstrated that cetuximab led to both improved local control and improved overall survival when compared to radiation alone, and this approach was not associated with increased acute or late toxicity with the exception of acneiform rash.[26,27] This study was the first of its kind in treating cancer of the head and neck, allowing evaluation of a molecularly targeted therapy in combination with radiation in the curative treatment setting. This study did not stratify patients on the basis of HPV status as this distinction was not appreciated at this time.

Following the radiation/cetuximab trial, the RTOG evaluated whether the addition of cetuximab to the standard chemoradiotherapy backbone of 70 Gy and cisplatin could further improve outcome (RTOG 0522). This phase 3 randomized trial of 70 Gy/cisplatin versus 70 Gy/cisplatin/cetuximab showed

no additional benefit over chemoradiotherapy alone and the addition of cetuximab was associated in this setting with increased overall toxicity.[28]

A current trial run by the RTOG (RTOG 1016, and similar studies in other countries) is addressing the question of whether cetuximab is effective in patients with HPV-positive cancer of the head and neck. This study randomizes patients with HPV-positive cancer of the head and neck to radiation + cisplatin versus radiation + cetuximab. Results of this prospective study will help define whether cetuximab can safely and effectively replace cisplatin in the treatment of HPV+ patients.

Human Papillomavirus

HPV-positive cancers arising in the oropharynx have been identified as a unique clinical, biologic, and epidemiologic entity that is associated with a significantly better prognosis than HPV-negative oropharynx cancers.[29–41] These significant differences have led to great interest in tailoring therapy to reduce treatment-related toxicity (i.e., deintensification).[42] A secondary analysis of the RTOG 0129 trial evaluated the prognostic implication of HPV in cancers of the oropharynx. The 3-year overall survival was 82% in the HPV-positive versus 57% in the HPV-negative patients.[29] A recursive-partitioning analysis classified patients with squamous cell carcinoma of the oropharynx into categories of low, intermediate, or high risk of death based on the following prognostic factors in decreasing order of importance: HPV, number of tobacco pack years, N stage, and T stage.[29] As noted above, RTOG is conducting a clinical trial randomizing HPV-positive patients between 70 Gy in 6 weeks with concurrent cisplatin versus 70 Gy in 6 weeks with concurrent cetuximab (RTOG 1016, NCT01302834).

Transoral Surgery

Transoral surgical approaches [i.e., transoral laser microsurgery (TLM) and transoral robotic surgery (TORS)] are garnering increased interest for the treatment of cancer of the head and neck.[43–45] A potential benefit of primary TLM and TORS for selected patients is a reduction in the intensity of chemoradiotherapy without compromising oncologic outcome. It is hoped that primary surgery will provide pathologic information to guide adjuvant therapy recommendations such that radiotherapy and chemotherapy may be

selectively omitted or reduced in intensity or that surgery will aid in treatment intensification for higher-risk patients.

There are several new clinical studies evaluating the use of TLM/TORS to alter treatment intensity. The Eastern Cooperative Oncology Group (ECOG) is enrolling early-stage HPV-positive oropharyngeal patients (ECOG 3311, NCT01898494). All patients undergo transoral resection (TLM or TORS) and then, based on pathologic features, receive risk-based adjuvant therapy: (1) patients with T1–T2 N0–N1 disease (negative margins, no extranodal extension) are observed, (2) patients with positive margins or extranodal extension receive 66 Gy with weekly cisplatin, and (3) intermediate-risk patients are randomized to 50 Gy or 60 Gy without chemotherapy. The primary end point is 2-year progression-free survival (PFS). This trial (and others under development) will help to provide standardization of methodology for transoral surgery in head and neck cancer and may have significant implications for the future clinical management of patients with oropharyngeal cancer.

The Basic Steps of Radiation Therapy Workflow

In this section, we provide an overview of the radiation oncology work process from pretreatment evaluation through posttreatment follow-up. Throughout this process, the radiation oncologist works with a team of specialists ranging from dentists to social workers to speech language pathologists to radiation therapists.

Pretreatment Assessment

The majority of patients with cancer of the head and neck are referred to radiation oncology by a head and neck surgeon. Multidisciplinary evaluation by head and neck surgery, medical oncology, and radiation oncology is an important initial step in the evaluation of patients with head and neck cancer. In our clinics, patients meet with the radiation oncology nursing staff prior to beginning radiation to discuss management of toxicity, oral hygiene, and skin care. They are provided a booklet containing recipes for oral rinses,

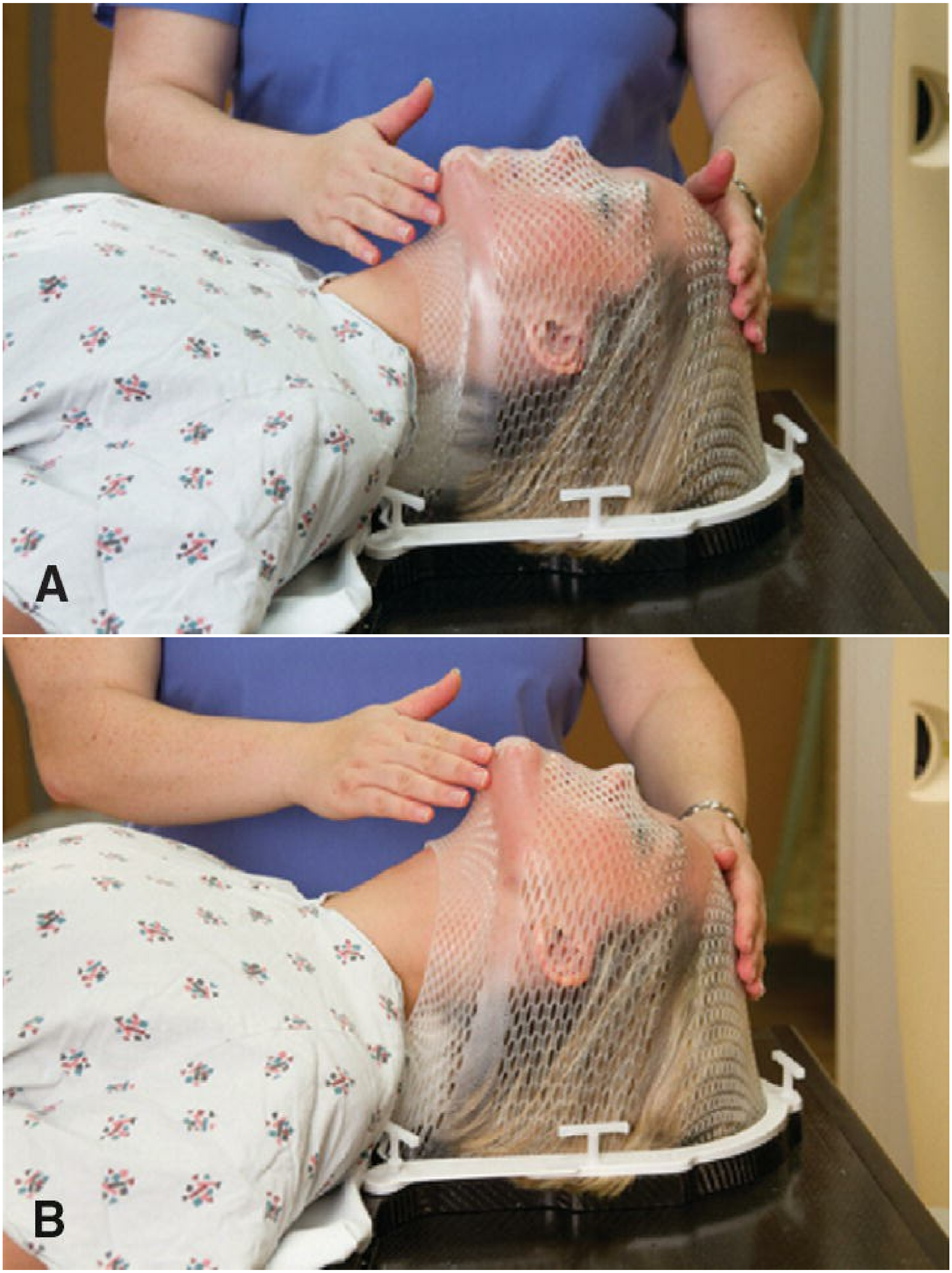
suggestions for skin care, and to address common questions.

It is our practice to routinely have patients seen for a dental evaluation prior to undergoing radiation. Radiation causes alterations in salivary function and oral microflora, which puts patients at increased risk for the development of radiation caries.[46,47] In addition, radiation can place patients at risk for the development of osteoradionecrosis, a potentially serious complication following dental extractions.[48,49] Dental evaluation may recommend fluoride trays to be used after radiation or prophylactic dental extractions should be considered before radiotherapy is initiated. In general, several days are allowed following dental extractions prior to the radiation planning computed tomography (CT) scan to allow for resolution of procedure-related edema. Radiation commences ~2 weeks after extractions to allow for adequate healing.

Patients undergoing radiation of the head and neck may develop odynophagia and/or dysphagia during treatment. These common side effects, if not caused by the cancer itself, often develop during the 2nd to 3rd week of radiation and progress until several weeks after the completion of radiation. Thus, for many patients, there is a 5- to 6-week period during which they have significant challenges maintaining adequate oral intake. Pretreatment evaluation by a speech/language pathologist with assessment of current swallowing function and a prescription for a series of exercises may decrease the long-term morbidity associated with radiation of the head and neck.[50–52] Still, a significant number of patients undergoing radiation for cancer of the head and neck or chemoradiotherapy will require supplemental nutritional support by way of a percutaneous endoscopic gastrostomy or nasogastric feeding tube placement. There exists considerable variation in tube placement with some centers routinely recommending prophylactic placement and others advocating a reactive approach. It appears that no difference in cancer outcomes is seen based on when feeding tubes are placed, that complications may be slightly higher for reactive placement, but that up to 30% to 50% of patients who undergo prophylactic tube placement will have minimal need to use it.[53–56] Most patients also meet with a nutritionist to discuss caloric needs, food choices, and the use of liquid nutritional supplements.

Simulation/Setup

The first step in the radiation treatment-planning process is to perform a simulation of the treatment setup. The majority of patients with cancer of the head and neck will have a CT scan with contrast in the treatment position with a plastic mesh mask made for immobilization of the head and neck. These thermoplastic (i.e., the plastic becomes soft and pliable when warmed and hardens as it cools to room temperature) masks can extend over the shoulders to provide immobilization of the entire head and neck region (Fig. 30.1). Optimal positioning of the patient requires oversight of the treating radiation oncologist to account for tumor location, normal structure anatomy, and individual patient variation. Following simulation, or at the time of the first treatment, patients may receive a permanent skin marking (“tattoo”) midline near the sternal notch that is used as a reference mark during daily treatment to align the patient in the correct position for treatment. Daily image-guided radiation therapy techniques are gradually reducing the need for skin markings. CT images are obtained of the area to be treated and this dataset is exported to the treatment-planning system. In most cases, the actual radiation start date will occur 7 to 14 days after this simulation to allow time for the subsequent steps to be completed. Occasionally, a CT simulation is not necessary (e.g., a superficial skin cancer), and instead, a clinical simulation is performed on the radiation treatment machine.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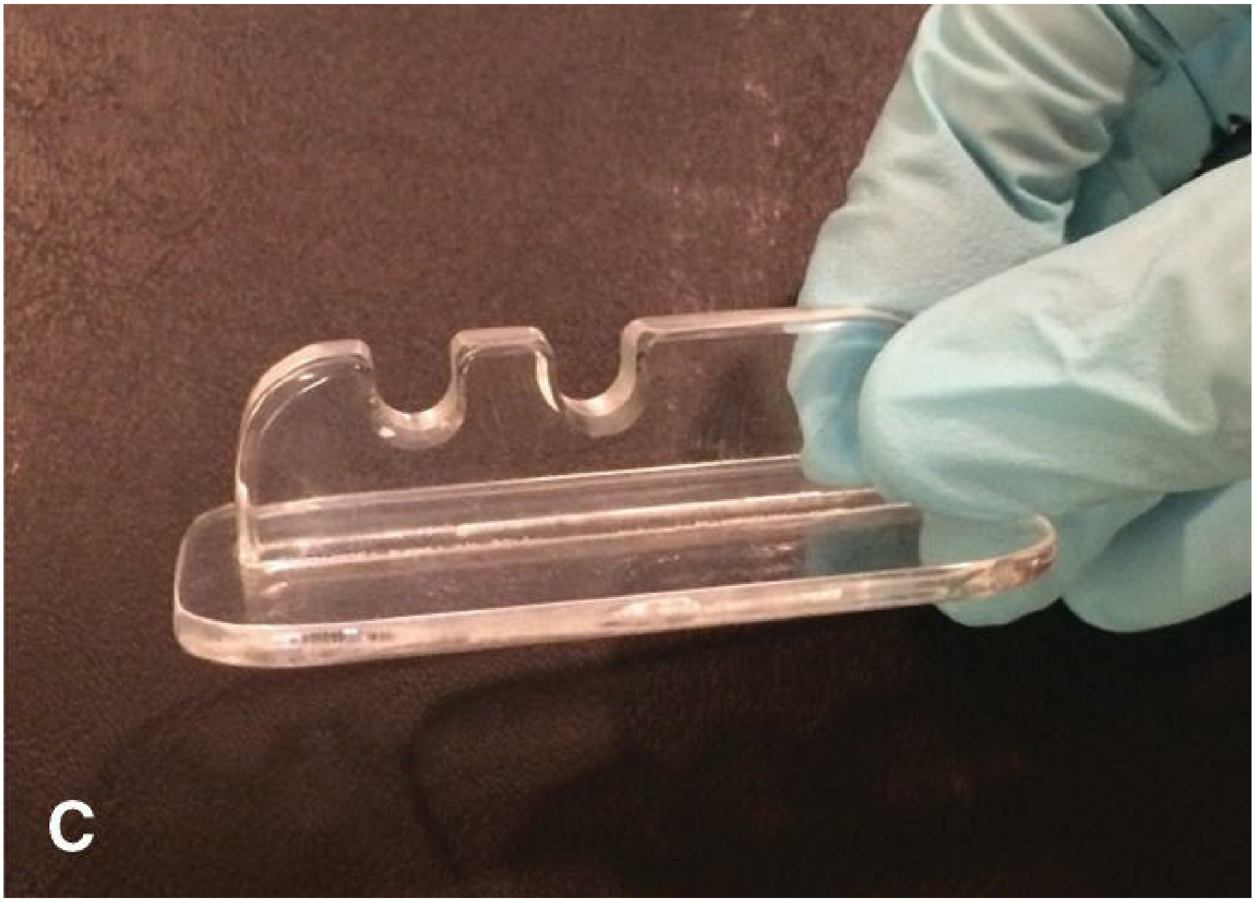


Figure 30.1. Patient setup. Patient immobilization and setup at the time of simulation is a critical step in the radiation treatment-planning process. **A:** Thermoplastic masks immobilize the patient with high reproducibility to minimize day-to-day variation in patient setup. **B:** Additional modifications that can be taken to position the patient include the use of different degrees of neck flexion. **C:** The use of bite blocks can provide spatial separation between critical structures and tumor.

Treatment Planning

Designing a radiation treatment plan is a multistep, iterative process. Representative contours and dose distributions are shown in Figure 30.2. Following the simulation, the radiation oncologist uses treatment-planning software to delineate target regions and avoidance structures (i.e., normal tissues). Modern intensity-modulated radiation therapy (IMRT) treatment planning begins with the radiation oncologist using the imaging studies [e.g., CT, positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI)], the physical examination (including fiberoptic

nasopharyngoscopy), and the pathologic information to identify the tumor and involved lymph nodes (gross tumor volume or GTV) and areas of subclinical tumor extension believed to be at risk for harboring disease (clinical target volume or CTV). The CTV may be further subdivided into high-risk and low-risk regions and differential radiation doses prescribed to each of these regions. The GTV and CTV are then uniformly expanded to account for setup variations and day-to-day differences in patient position to form a planning target volume (PTV). In the past, many centers used weekly patient position verification checks, and thus, PTV expansions of 1 cm were not uncommon. With the use of daily image guidance, PTV margins have been safely reduced to the 3- to 5-mm range, significantly decreasing the volume of normal tissue treated. Critical normal structures (e.g., parotid glands, submandibular glands, brainstem, cochlear apparatus, globe, lens, oral cavity, larynx, esophagus, mandible, pharyngeal constrictors, and spinal cord) are also contoured for dose reduction. The radiation oncologist then enters a treatment-planning order. This written directive defines the desired dose to be delivered to target structures (e.g., GTV + 3 mm = 70 Gy, $CTV_{intermediate}$ = 60 Gy, $CTV_{lowrisk}$ = 50 Gy) and the dose constraints to critical normal structures (e.g., mandible <70 Gy, spinal cord <45 Gy).[57–64] The planning process is then transferred to a dosimetrist who will arrange beams and refine the delivery of radiation to meet prescribed goals with physicist oversight. Physician review of the dose distribution is then carried out on cross-sectional imaging viewed in the axial, coronal, and sagittal planes with evaluation of dose volume histograms (DVHs) that graphically depict each target or avoidance structure and the dose received by percentage of the total volume (Fig. 30.3). If any metrics are unsatisfactory, an iterative process is used to further refine the treatment plan until an acceptable one is identified. Approval of the final plan precedes the next step of quality assurance checks to ensure that the machine is capable of delivering the designed plan and that the dose delivered meets the prescription dose. Only after each of these steps is completed is the plan ready to be delivered to the patient.

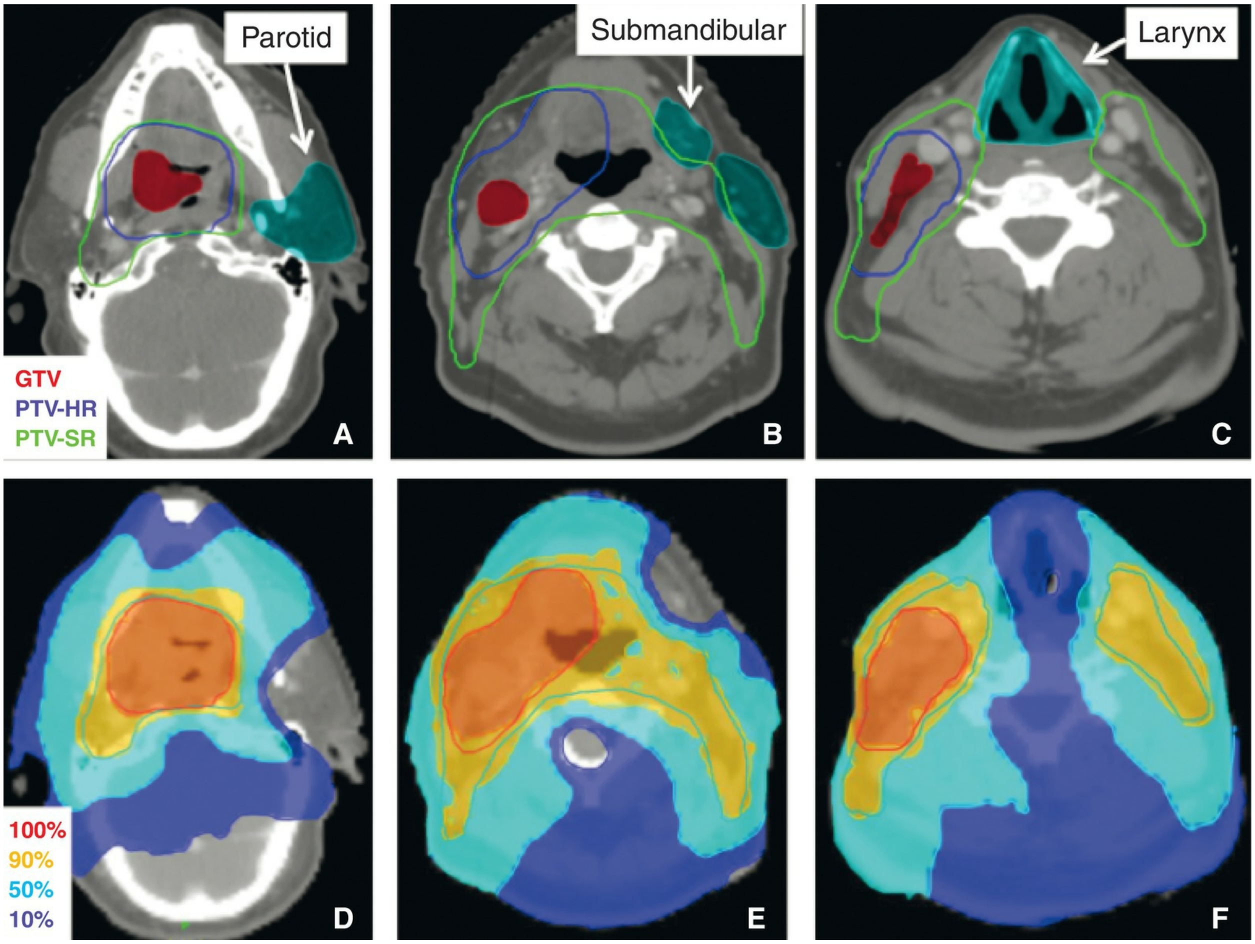


Figure 30.2. Representative IMRT plan for a patient with a T2 N2b M0 squamous cell carcinoma of the tonsil. Panels **A** to **C** show the delineated normal tissues and target volumes. Panels **D** to **F** show the isodose distribution from the IMRT plan. Note that the parotid, submandibular, and larynx are spared. (GTV, gross target volume; PTV-HR, planning target volume-high risk; PTV-SR, planning target volume-standard risk.)

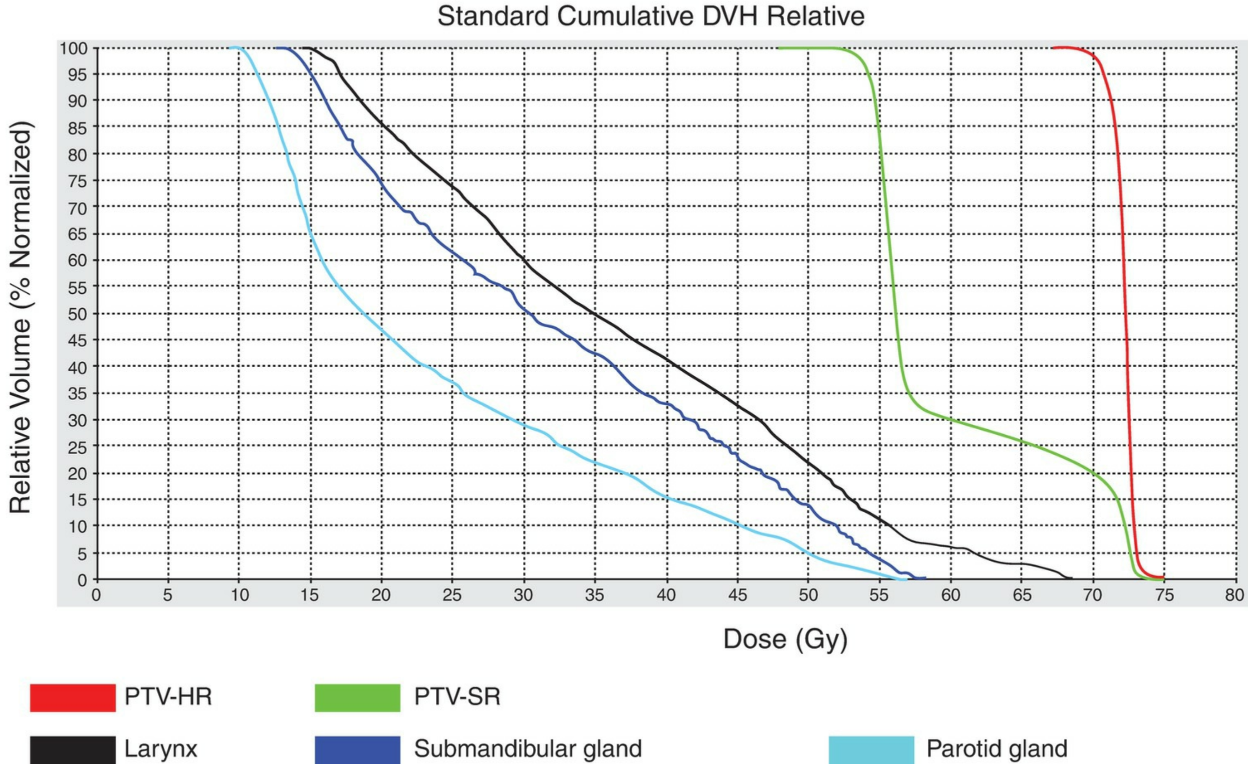


Figure 30.3. DVHs relate radiation dose to tissue volume. Graphical representation of dose to volume is provided by a DVH but do not provide spatial context as to the location of the dose within a given tissue. For most PTVs, more than 95% of the volume should receive at least 95% of the dose. Depending upon the normal structure, the median or maximal dose has greater relevance to potential toxicities.

It is important to note that when requesting outside radiation records for review, one should ask for the DVH's and isodose distribution on cross-sectional imaging. The treatment summary should also be reviewed, but this typically does not include the graphical information required to understand the complex three-dimensional dose distributions delivered using current techniques. Historically, portal radiographs (a.k.a. port films) would also be requested. These provide a view of the treated field from the machines point of view but are of limited relevance in an IMRT plan.

Quality Assurance/Control

The sophistication and complexity of clinical treatment planning and delivery has increased significantly over the last 20 years. This complexity is managed, in part, through overarching quality assurance/control programs

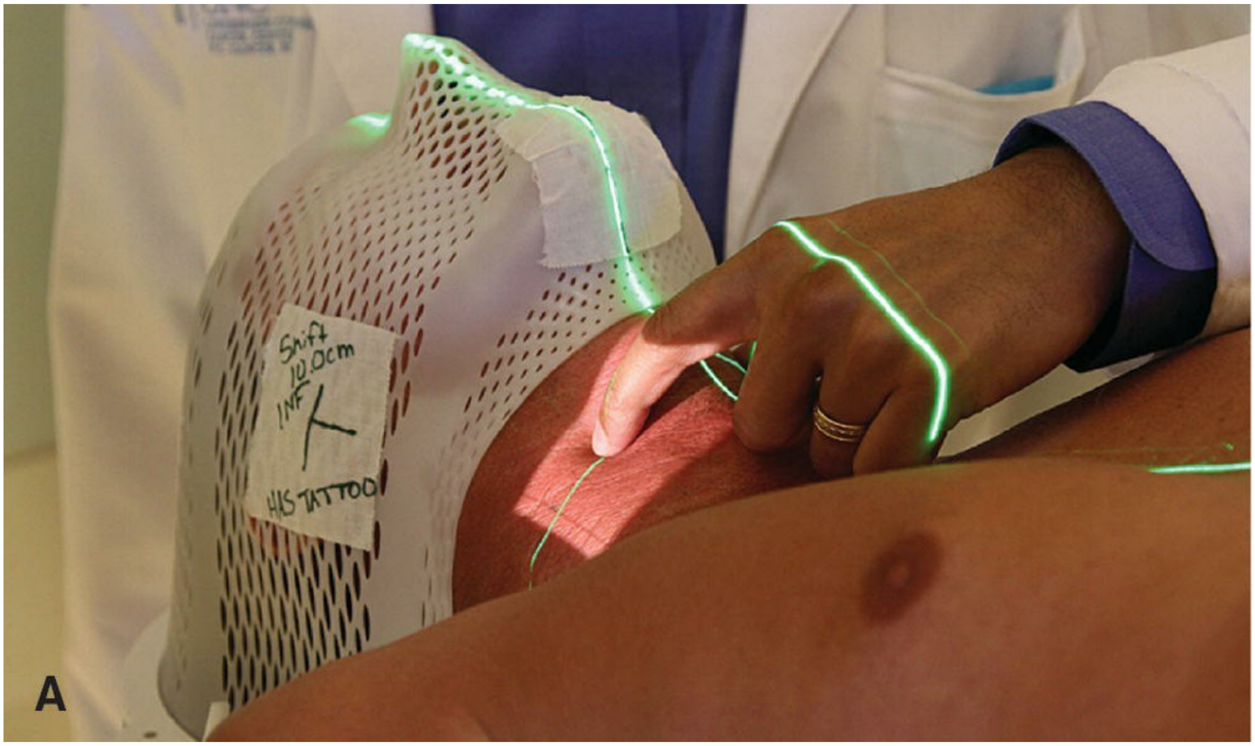
that are typically managed by medical physicists working directly with the radiation oncologist. The role of the medical physicist in quality assurance begins before the patient ever enters the radiation oncology workflow and continues until the treatment is completed (Table 30.2). Encompassing multiple steps in the process, quality assurance is performed to regulate and validate each step in the process with the ultimate goal of ensuring the accurate and precise delivery of radiation treatments.

Table 30.2 The Role of Quality Assurance in Radiation Therapy
Patient positioning and immobilization
Image acquisition and input
Anatomy definition
Beam/source technique
Dose calculations
Plan evaluation
Plan implementation
Plan review
Posttherapy recording

Daily Imaging

During treatment, a patient's setup is verified with onboard imaging technology that is part of modern linear accelerators (LINACs; Fig. 30.4). Although the images that are obtained on the LINAC are not the same quality as diagnostic images, they are adequate to verify the accuracy of patient setup. Verification imaging is typically performed weekly, biweekly, or daily. Historically, with two-dimensional and three-dimensional radiation plans, "PORT" films, which are plain radiographic films of the actual treatment fields transposed on the patient's skeletal anatomy, were performed (Fig. 30.4C). In the modern IMRT era, daily imaging with onboard CT technology is commonly used. The onboard CT images are registered, or fused, with the

CT simulation images at the treatment console at the time of treatment and offsets are made to correctly align the patient (Fig. 30.4D).

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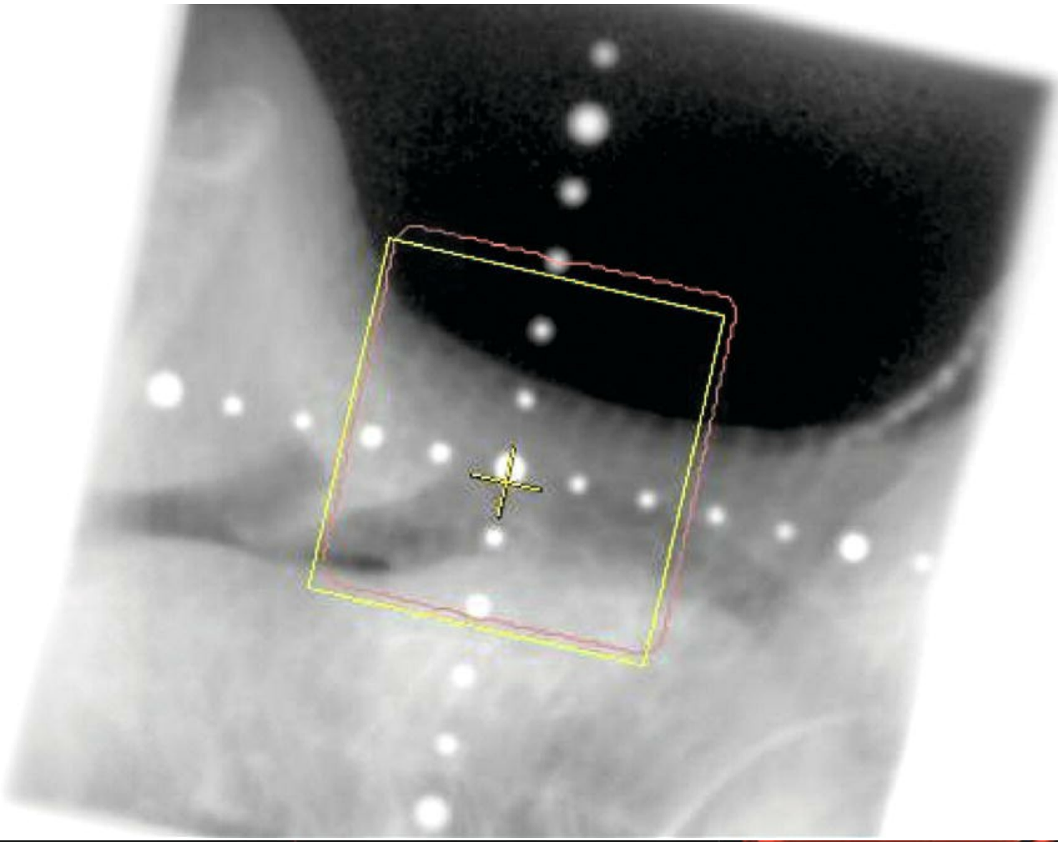

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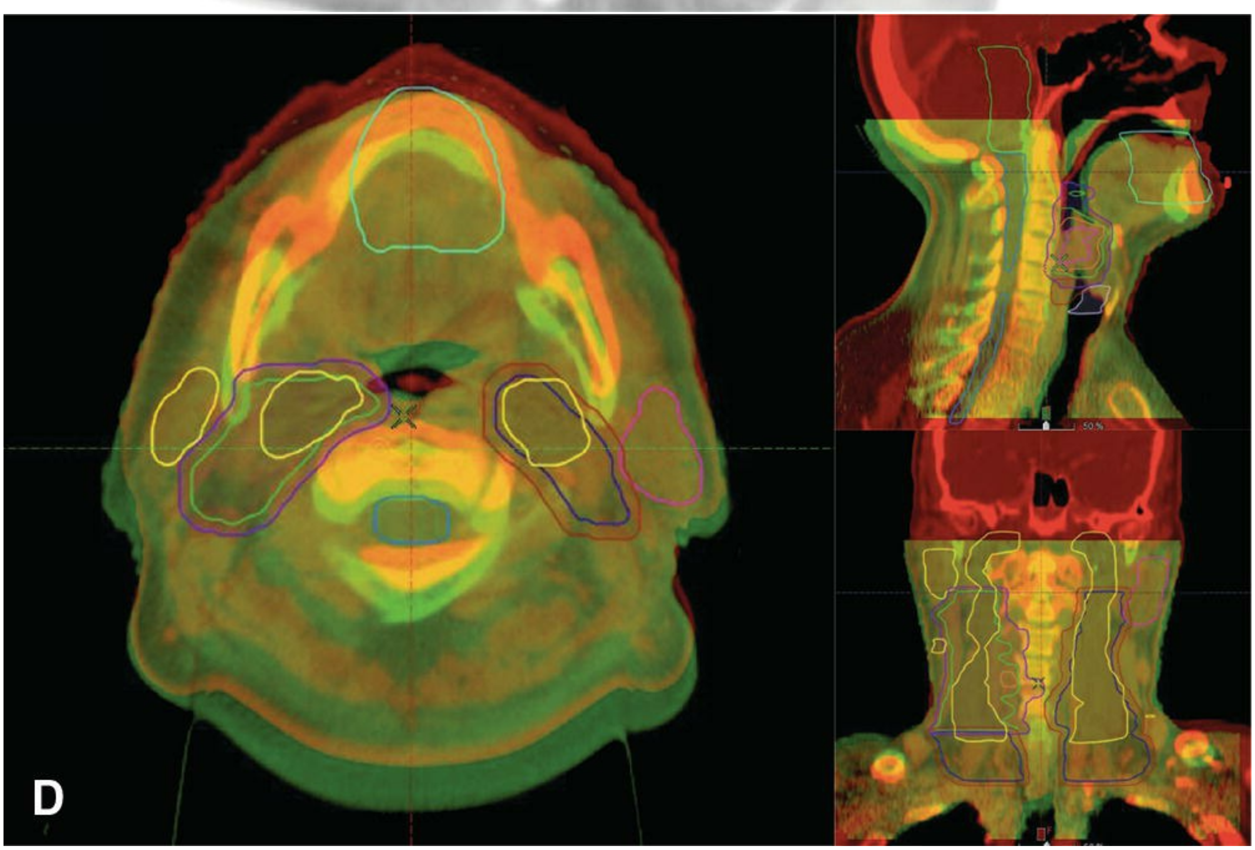

D

Figure 30.4. Setup and verification of patient positioning. **A:** Initial patient

setup can be verified by physical exam and a set of precision positioning lasers. **B:**The treatment-planning software creates a virtual x-ray or digitally reconstructed radiograph (DRR) projecting the treatment field onto the patient as shown for this patient with a T1N0 vocal cord cancer. **C:** The DRR is then matched to a portal imaging films to ensure that the patient is properly aligned prior to treatment. **D:** Daily imaging is most commonly performed using cone-beam imaging, which involves production of a CT image (*yellow shades*) and matching patient position to the original planning CT scan (*red shades*).

Weekly Management

Each week during treatment, the patient is seen by the radiation oncologist to review the progress of treatment, manage acute toxicities, and preemptively address expected toxicities. The weekly check or on-treatment visit (OTV) is an important part of the radiation oncologist's management of the patient and involves not only a directed history and physical exam but also review of labs and assessment of any needed changes in the overall treatment plan. For patients with cancer of the head and neck, this visit often includes a visit with a nurse or nutritionist to maximize nursing and nutritional support. Of course, as needs arise on other days, toxicity management and patient counseling can occur throughout the course of radiation.

Posttreatment Follow-up

Most patients are seen for a brief posttreatment follow-up visit within the first month after completing radiation. The purpose of this visit is to assess response to treatment, continue management of acute toxicities, and plan further follow-up visits. Most acute toxicities of treatment (e.g., skin erythema and desquamation, mucositis, fatigue, odynophagia, dysphagia) nadir 10 to 14 days following completion of radiation and are improving gradually by 4 weeks posttreatment. Some toxicities (e.g., xerostomia, dysgeusia) take significantly longer to resolve. For most patients with cancer of the head and neck, a posttreatment imaging assessment occurs 8 to 16 weeks following the end of treatment to allow for resolution of acute toxicities and inflammation induced by radiation. Follow-up visits then occur every 2 to 3 months in the first year, every 3 to 4 months in the 2nd year, every 3 to 6 months through year 5, and yearly thereafter. Due to radiation

effects on the thyroid, thyroid-stimulating hormone (TSH) levels should be checked regularly and replacement levothyroxine prescribed, as necessary. Multidisciplinary follow-up, alternating between the head and neck surgeon, medical oncologist, and the radiation oncologist, is an important component of long-term survivorship and multidisciplinary care.

Basic Radiation Treatment Delivery Approaches

2-D/3-D

Clinical and plain radiograph–based two-dimensional radiotherapy use findings from the physical or endoscopic examination to delineate regions at risk to target radiotherapy delivery. With the advent of CT-based imaging, conformal three-dimensional approaches can be used to shape the radiation field to the individual patient and their tumor. These plans often used parallel opposed fields to deliver a homogeneous radiation dose. The use of multiple angles from which the radiation dose is delivered results in improved conformality of the dose to the true target. With the advent of IMRT techniques, these “conventional” techniques are less commonly used at most centers today.

Intensity-Modulated Radiation Therapy

Advances in the ability to modulate beam intensity and delineate the tumor with greater accuracy make it possible to deliver radiation doses to three-dimensional volumes that conform to the shape of the target tissue and limit dose to critical normal structures. IMRT is now the preferred radiation treatment technique for the majority of cancers of the head and neck. IMRT uses multiple radiation beams from various directions and creates steep dose gradients and highly conformal dose distributions resulting in strong coverage of tumor and high-risk targets while maximizing the ability to limit total dose to normal tissues.

For IMRT treatment planning, the radiation oncologist delineates (i.e., contours or identifies on cross-sectional imaging) the GTV(s), CTV(s) (GTV

+ a margin accounting for subclinical disease), and PTVs (CTV + a margin for setup error on the radiation machine). In addition to these target regions, the radiation oncologist also delineates normal organs at risk. These structures are included in the radiation planning software with constraints to limit the dose delivered to them with the goal of improving functional outcomes or limiting morbidity (e.g., spinal cord, larynx, brainstem, salivary glands). Figure 30.2 shows a representative IMRT plan with contoured targets and isodose distributions.

Brachytherapy

Brachytherapy is the delivery of radiation by radioactive sources placed within the tumor. Brachytherapy is often combined with external beam therapy to selectively boost the primary tumor to higher dose while minimizing exposure of surrounding normal tissues. Brachytherapy used in patients with cancer of the head and neck can take several forms.[65] Interstitial implantation for cancer of the tongue, floor of the mouth, or lip involves the temporary placement of multiple hollow catheters into the tumor bed.[66,67] Radioactive sources are then placed within these catheters to deliver the prescribed dose. Mold brachytherapy can be used for lesions of the hard palate or skin whereby a customized surface applicator with built-in channels for radioactive catheters is placed overlying the lesion.[68–70] Mold brachytherapy can provide superficial doses, and thus, its use is primarily valuable for superficial lesions where deep dose penetration is not required. Intracavitary applicators have been used to deliver radiation to regions such as the nasopharynx and are most commonly used for recurrent nasopharyngeal carcinoma.[71,72] Improvements in conformal external beam radiation techniques including IMRT and proton therapy have gradually reduced the use of brachytherapy for many patients with cancer of the head and neck.

Intraoperative Radiation Therapy

Intraoperative radiotherapy (IORT) provides a steep dose falloff to spare normal tissues and is typically delivered to the tumor bed following a gross total or near total resection (reviewed in[73]). Delivery of IORT is typically done through the use of electrons or a high–dose rate, low-energy photon source such as Ir-192. Electrons are delivered via a LINAC or, more recently,

using mobile electronic sources. Retrospective reviews of IORT for treating patients with cancer of the head and neck have shown low rates of surgical wound complications.[74–78] Delivery of IORT requires coordinated multidisciplinary care with the surgeon and radiation oncologist working together to identify critical structures and sites of microscopic residual cancer in order to provide the optimal treatment. The common clinical use of IORT is for patients with isolated, resectable, regionally recurrent disease who have previously received external beam radiation therapy.

Basic Radiation Physics

A complete description of the physics of radiation therapy is beyond the scope of this chapter. A good reference for those interested is *The Physics of Radiation Therapy* by Khan.[79] In this section, we provide a brief overview of x-rays, electrons, protons, and several other types of radiation.

Electromagnetic Radiation

The most commonly used type of radiation involves high-energy x-rays or gamma (γ) rays, commonly referred to as photons. Both x-rays and γ-rays have similar physical and biologic properties and differ primarily in how they are produced. X-rays are generated by LINACs, which use electricity to accelerate electrons toward a metal target (typically tungsten). As high-speed electrons pass close to the nuclei of the tungsten target, negatively charged electrons are attracted to the nucleus, lose energy, and are deflected or accelerated. The energy loss is radiated as a high-energy photon. γ-rays are emitted by fission of radioactive isotopes such as cobalt or iodine. Today, most modern radiotherapy is delivered using high-energy x-rays produced by LINACs. One relevant exception to this that is important to the head and neck oncologist is the use of radioactive iodine for the treatment of cancer of the thyroid.[80,81]

The unit of absorbed dose in tissue is the centigray (cGy) with 100 cGy equal to 1 gray (Gr). Doses of protons and neutrons are typically reported as gray equivalents. For a more complete review of absorbed dose and the details of radiation physics, the reader is referred to *The Physics of Radiation*

Therapy.[79]

Electrons

Electrons are small, negatively charged particles that can be accelerated to high energy by a LINAC. Electrons exhibit favorable depth dose characteristics with a finite range, relatively rapid dose deposition and falloff, and higher surface dose (Fig. 30.5A). Electron beams are widely used for the treatment of superficial lesions such as cancer of the skin or in an intraoperative setting for exposed tumor beds. Electrons are also produced by LINACs by removing the tungsten target out of the path of the original high-speed electrons produced in the head of the LINAC.

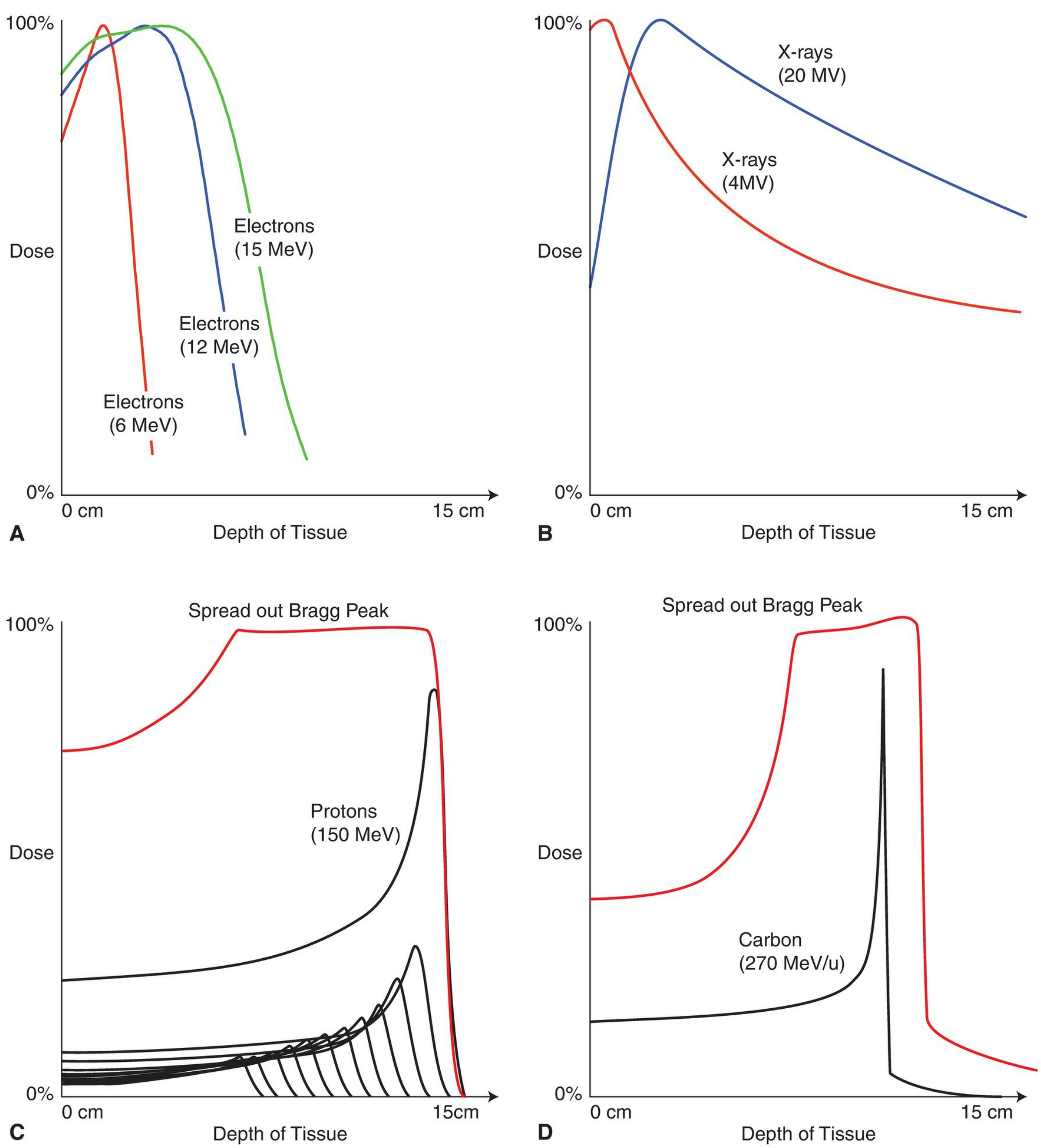

Figure 30.5. Depth dose characteristics of radiation modalities. **A:** Electron beams exhibit high entrance dose and rapid dose falloff with depth. Higher-energy electrons deliver both higher surface dose and deeper penetrating ability. **B:** Photons whether derived from LINACs (x-rays) or from radioactive sources (γ-rays) are more penetrating than electrons. Increasing photon energy results in more surface sparing, deeper maximal dose, and greater penetration. **C:** Protons exhibit a Bragg peak resulting in significant

dose deposition at depth. The spread out Bragg peak increases entrance dose in order to treat a significant volume. Little exit dose results from proton radiation, but there is a degree of uncertainty regarding the true stopping point of protons. **D:** Heavy ions such as carbon or helium exhibit greater stopping certainty, lower entrance doses, and greater biologic effectiveness compared to protons. Similar to protons, a spread out Bragg peak increases entrance dose.

Photons

The majority of radiation treatments to the head and neck consist of high-energy x-rays generated by a LINAC. Therapeutic and diagnostic photons differ in their energy with therapeutic photons being in the megavoltage (MV) range whereas diagnostic photons are in the kilovoltage (KV) range. The higher the energy, the deeper the penetration of the radiation dose (Fig. 30.5B). The most commonly used energy x-ray beam is 6 MV, the energy that is used in most IMRT plans. Photons deposit energy and thus radiation dose by liberating electrons from the outer shells of atoms. These energized electrons interact with other particles, resulting in energy transfer and the generation of free radicals leading to cell death (see section on Radiation Biology).

Particle Radiation

Particle therapy (i.e., protons, neutrons, or heavy ions) is used less often than photons and electrons for the treatment of cancer of the head and neck. Due to the higher mass of particles, either a cyclotron or a synchrotron is required to accelerate particles to relevant speeds. Due to this expense associated with installation of these centers, particle therapy installations are limited in number.

Protons

Protons are positively charged particles that deposit relatively constant dose until they reach the end of their range where the majority of dose is deposited in a Bragg peak (Fig. 30.5C) with rapid subsequent falloff. The ability to modulate the depth of proton dose deposition results in advantages in the treatment of tumors located close to critical organs including skull base

tumors, choroidal melanomas, and a number of pediatric malignancies. Proton therapy centers have proliferated over the last several years in the United States and are now used in the treatment of a variety of malignancies. The ultimate clinical benefit of improved physical dose distribution from proton therapy remains to be determined and several clinical trials addressing this issue are currently ongoing.

Neutrons

Neutron irradiation, which exhibits different biologic effects than electrons, photons, or protons (discussed below), has been used in the past to treat a number of different cancer types. The use of neutrons has been limited due to the small number of centers with the necessary technology and to the fact that efficacy has only been documented in tumors of the salivary gland.

Heavy Ions

Other types of particle radiation (e.g., α-particles, negative π mesons, and heavy charged ions such as carbon or helium) exhibit depth dose distributions that may prove even more favorable than protons (Fig. 30.5D) and continue to be studied at a small number of specialized centers around the world.

Basic Radiation Biology

For the interested reader, a thorough examination of radiation biology is available in *Radiobiology for the Radiologist* by Hall and Giaccia.[82] Radiation induces pleiotropic effects on affected tissues including both normal tissues and tumors. In general, the mechanisms of cell death due to radiation vary based upon the type and dose of radiation. All types of radiation cause breaks in chemical bonds. These breaks can occur either as a direct consequence of the radiation or indirectly via the generation of free radicals (Fig. 30.6A). Radiation delivered via neutrons, α-particles, or heavy ions exerts the majority of their effects via direct damage. The more commonly utilized electrons or photons exert approximately two-thirds of their effects via indirect mechanisms.

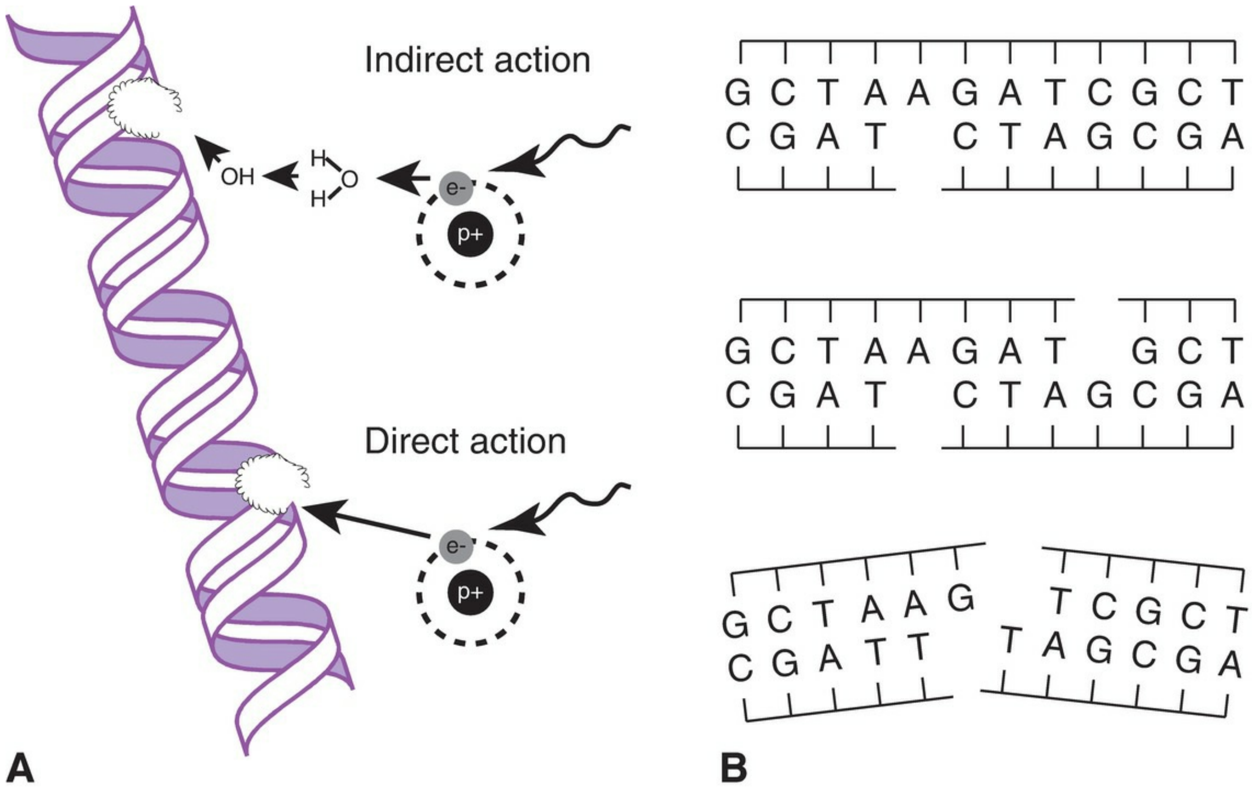

Figure 30.6. Schematic of DNA demonstrating direct and indirect effects of radiation. **A:** Schematic demonstrating the direct and indirect actions of radiation with DNA. An incident photon is absorbed by an atom of DNA producing a secondary electron and directly damaging the DNA (**top**). Indirect action involves photonic effect upon a secondary molecule (often water) to produce a free radical such as hydroxyl (OH•), which then produces damage to the DNA (**bottom**). **B:** Generation of single-strand breaks (**top**) are easily repaired using the opposite strand as a template for repair. Breaks in both strands that are separated by enough distance are repaired independently (**middle**). When two breaks occur opposite each other, or separated by only a few base pairs, double-strand breaks occur (**bottom**). Double-strand breaks can result in duplications, abnormal chromosome structure, lost chromosome segments, or error-prone repair and often have significant consequences.

Radiation-Induced Cell Killing

Radiation-induced cell death is classically modeled by the linear-quadratic equation. This model calculates the survival probability of a given cell as a function of the overall radiation dose, the dose per fraction, and the overall

treatment time.[83] The dose response of both tumors and normal tissues can be described according to the α/β ratio, which is an indication of the sensitivity of a particular cell type to different radiation fraction sizes. The α/β for most tumors and for "early-responding" normal tissues such as skin and mucosa is high (≥10), whereas for "late-responding" normal tissues such as spinal cord and brain, it is low (≤5).[84] One important implication for this difference between tumor and critical normal tissues is that different fractionation schemes can be used to modulate the therapeutic ratio to improve outcome. Cells injured by radiation can die in several distinct ways: mitotic death, senescence apoptosis, or via immunogenic cell death. Each of these is discussed briefly below.

Mitotic Cell Death

Mitotic death occurs when cells with damaged DNA attempt to divide. Depending upon the radiation dose, cells may die either at the first postradiation cell division or after several apparently normal cell divisions. Thus, irradiated cancer cells may continue to die days to weeks after the final radiation dose is delivered. This simple feature underlies the rationale for waiting 8 to 10 weeks after completing therapy prior to assessing response with cross-sectional imaging or biopsies. Mitotic cell death occurs due to aberrations in DNA induced by radiation (Fig. 30.6B). Single-strand breaks in DNA are the most common type of damage but are easily repaired. Double-strand breaks can result in chromosomal aberrations (e.g., ring chromosomes, dicentric chromosomes, acentric fragments, etc.) and are considered the main molecular events preceding mitotic cell death. Mitotic cell death has been thought to be the primary mechanism of radiation-induced cell death for many years, although more recent data suggest that apoptosis and immune-mediated cell death also play important roles.

Apoptosis

Radiation-induced apoptosis occurs in all types of cancer but is most commonly seen in lymphomas and other rapidly dividing tumors. Unlike mitotic cell death, apoptosis usually occurs within hours of radiation and can be seen after relatively low doses of radiation. Apoptosis, a form of programmed cell death, is an orderly process by which cells undergo a defined set of biochemical steps including endonuclease activation,

chromatin condensation, cellular shrinkage, and cellular fragmentation. These cellular fragments are phagocytosed by adjacent cells or macrophages eventually leaving no cellular debris. In addition to contributing to tumor cell death, apoptosis has also been described in both salivary and lacrimal gland tissues[85]–[87] and can thus contribute to xerostomia and xerophthalmia early during the course of radiation.

Immunogenic Cell Death

Enhanced tumor-specific immunity induced by radiation is a concept that has gained attention in recent years as accumulating evidence supports its relevance in the clinical setting and novel agents capable of enhancing this effect have been identified.[88,89] The interaction of radiation with the immune system is complex and remains the subject of ongoing study. Locally and systemically, radiation induces a cascade of pro immunogenic effects (e.g., release of tumor antigens, upregulation of cytokines, etc.), which have been observed to result in immunogenic cell death (i.e., antitumor immunity). Radiation-mediated cell death may trigger uptake of antigenic compounds by dendritic cells thus stimulating antigen-specific cytotoxic T lymphocytes (CTLs) and production of tumor-specific antibodies. These CTLs can then target tumor tissue both within the irradiated mass and potentially at sites of distant disease. The response of tumor distant from the irradiated field is termed the abscopal effect and was first described over 50 years ago.[90] The use of immune-modulating therapies may augment this effect.[91,92]

Radiation Effects on Cells and Tissues

Radiation can impart effects on patients at the cellular, tissue, and organ level. Cellular responses to radiation play a major role in the acute effects of cancers and normal tissues. The organization of organs into parallel or serial systems is an important determinant as to whether dose to a single point (maximal dose) or dose to the entire organ (mean dose) plays a more important role in the organ response to radiation.

Cell Kinetics

Radiation results in numerous cellular responses that impact upon the cell cycle by affecting the expression of proteins that regulate cell cycle

progression. In general, these responses result in cell cycle arrest or mitotic delay, providing the irradiated cell time to repair damage to DNA and cellular organelles. The duration of this mitotic delay depends on the radiation dose, dose rate, cell type, and the preradiation cell cycle phase.

Radiation is also known to affect the proliferation rate of both normal and cancer tissues. Removal of cells by chemotherapy, radiation, or surgical resection can trigger a regenerative response through a process known as **accelerated repopulation**. This process results in an increase in cell division that varies greatly among tissues and tumors. In general, tissues with rapid cell turnover (e.g., mucosal epithelial cells and tumor cells) exhibit early onset of repopulation. This response in normal tissues helps to speed the recovery of injury. Unfortunately, within tumors, accelerated repopulation can reduce the likelihood of cure through progressive tumor growth and is exemplified by the importance of overall treatment time on local tumor control. It is also thought to underlie the potentially beneficial effects of accelerated or twice daily radiation although the magnitude of this effect may be partially overcome by the concomitant delivery of chemotherapy.[93]

Tissue Effects

Most normal tissues are able to tolerate moderate radiation doses without losing structural integrity or function. Tissue injury occurs when sufficient numbers of cells are killed such that mature cells can no longer be replenished. The timing of damage depends upon both the organizational structure of the affected tissue and its cellular kinetics. Discussions of tissue damage often divide effects into acute, subacute, or late/chronic responses.

Tissues with a small number of slowly proliferating stem cells that produce rapidly proliferating progenitor cells exhibit toxicity within days or weeks after the initiation of radiation. Examples include the epithelial cells of the mucosa and skin. Radiation-induced injury of these cells occurs within a predictable time frame that is approximated by the life span of the mature cells. These tissues can recover essentially all of their functions when sufficient stem cells survive to reconstitute the depleted cellular compartments.

Subacute effects occur weeks to months after radiation in tissues with long cellular turnover times and are generally reversible. Examples include

Lhermitte syndrome, pneumonitis, and somnolence following radiation of the spinal cord, lung, and brain.

Late responses occur in tissues with very low cellular turnover including the bone, soft tissue, nervous system, and endocrine tissues with resulting complications including osteonecrosis, fibrosis, trismus, myelopathy, and endocrine dysfunction. These responses can occur years after radiation and are highly dependent upon radiation dose. Radiation regimens have been designed to minimize these serious complications to the extent possible.

Radiation Sensitivity

The radiation sensitivity of cells, tissues, organs, individuals, and tumors has important implications for their treatment and the side effects and toxicities that can be expected. Measurement of radiation sensitivity in vitro does not necessarily correlate with sensitivity in vivo due to built-in redundancies in tissues and organs and to the importance of the cellular microenvironment for individual cell responses.

Measurements of Radiation Sensitivity

The ability of a single cell to grow into a colony that can be easily seen is strong evidence that the cell has retained reproductive integrity. This type of assay (i.e., a colony formation assay) has for many years been considered the gold standard for in vitro radiation sensitivity studies (Fig. 30.7A). Typically, a colony consists of at least 50 cells or more than 5 cell divisions from a single-plated cell (25 = 32 cells). Colony formation assays are plotted on semilogarithmic axes with radiation dose plotted on the linear *x*-axis and surviving fraction on the logarithmic *y*-axis. Use of semilogarithmic axes results in a straight line for an exponential process whereby a doubling of radiation dose results in a reduction in the surviving fraction by 50%. A number of different mathematical models have been used to describe the characteristic shape of the cell survival curve. Overall, the most commonly used model across a range of radiation doses is currently the linear-quadratic model.[94]

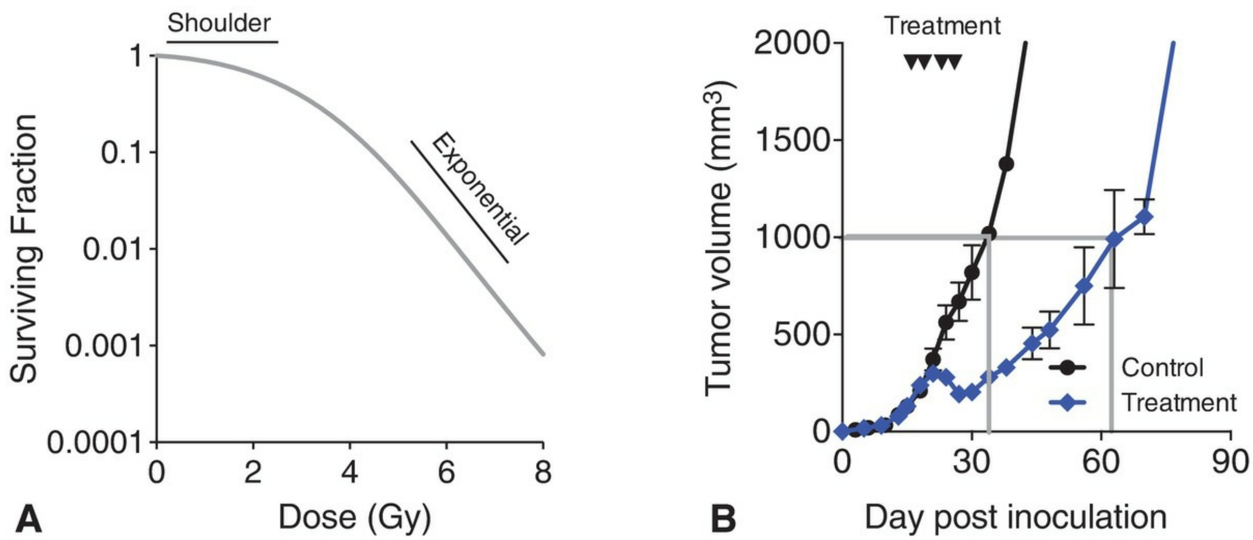

Figure 30.7. Radiation survival assays. **A:** Colony formation assays are graphed on a semilog plot and commonly demonstrate a shoulder region, an exponential decline, and can be modeled using a linear-quadratic model. **B:** Tumor growth delay can be reported using in vivo models and is calculated by determining the excess time required for a treated tumor to reach a predetermined size relative to the control tumor.

In vivo radiation sensitivity can be evaluated using a variety of different assays. The most common of these is the tumor growth delay assay in which in vivo growing tumors are irradiated and the difference in time to reach a predetermined tumor size is calculated (Fig. 30.7B).[95] Tumor control assays utilize large numbers of mice treated with a range of relatively high radiation doses to determine the proportion of tumors that are locally controlled to determine the dose required to "cure" 50% of tumors (TCD_{50}).[96] Several other techniques of assessing radiation sensitivity in vivo have been used including lung or spleen colony formation,[97] in vivo radiation/in vitro colony formation, and dilution assay but are not further discussed here.[98]

Factors Affecting Radiation Sensitivity

Significant work is ongoing to understand biologic, epigenetic, and physical factors affecting radiation sensitivity. However, several factors including tumor oxygen levels, germline patient variations, tumor etiology, and the type of radiation bear mention here due to their importance in head and neck oncology.

Powerful in its effect and extraordinarily simple in its action, oxygen represents the most potent modulator of radiosensitivity. Over 100 years ago, the effect of limiting oxygen was first described from simple models of skin erythema. Oxygen exerts its effect by altering how cells process radiation-induced free radicals and, importantly, must be present within milliseconds of the radiation exposure. As radiation travels through tissue, ion pairs are produced. These ion pairs have very short life spans and produce free radicals (i.e., molecules with an unpaired electron). These free radicals break chemical bonds that can either be repaired through reaction with a sulfhydryl group or made permanent (i.e., fixed) by the formation of anorganic peroxide (RO_2), a reaction that requires oxygen. The oxygen effect increases with oxygen concentration in the range of 0 to 20 mm Hg, but beyond this level, further increases have little additional effect. Adequate oxygenation results in a two- to threefold increase in the effect of radiation compared to hypoxic conditions.

Consistent with the importance of oxygen, the presence of hypoxia in cancers of the head and neck is associated with poorer outcomes.[99–101] Several prospective trials have investigated the effect of hypoxic modification in head and neck cancer. The use of a hypoxic modifier (nimorazole or tirapazamine) results in improved local–regional control.[102,103] Other groups have attempted to improve tumor oxygenation by treating anemia; however, this approach has not proven successful. In one randomized study, patients treated with erythropoietin had improved hemoglobin levels but worse cancer outcomes.[104]

Factors intrinsic to the patient and the tumor also affect radiation sensitivity. For example, patients with ataxia–telangiectasia demonstrate abnormal sensitivity to ionizing radiation that can result in greater than expected toxicity due to radiation therapy.[105] From a tumor standpoint, we and others have recently provided preclinical data suggesting that patients with cancer of the head and neck caused by HPV have increased sensitivity to radiation,[106,107] a result that may partially underlie the improved outcomes seen in this group of patients.[29,34,36,40,103,108–112]

Finally, different types of radiation can deposit differing amounts of energy. Linear energy transfer (LET) is a measure of the energy deposition per track length (i.e., distance). X-rays/γ-rays, electrons, and protons are all

considered low-LET radiation and induce similar amounts of damage per gray. Neutrons and heavy nuclei (e.g., carbon or helium) produce a stronger biologic effect per dose and are referred to as high-LET radiation. High-LET radiation not only induces greater damage in tumors but also causes greater damage in normal tissues. Currently, high-LET radiation is only delivered at a handful of centers around the world (discussed in Reference 113), and although neutron therapy has shown a benefit over photon radiotherapy for the treatment of salivary tumors in a randomized trial,[114] the modality is not commonly used due to the dearth of neutron centers worldwide.

Biology and Physics in the Clinic

Over the last century, fractionation (delivery of multiple small doses of radiation) has become the most common way to deliver therapeutic radiation. Although exceptions such as stereotactic radiosurgery (SRS), stereotactic body radiotherapy (SBRT), and stereotactic ablative body radiotherapy (SABR) are being used more frequently in a variety of disease sites, fractionated therapy remains the mainstay of radiotherapy for head and neck cancer. Four well-known biologic processes underlie the use of fractionated therapy. Often referred to as the four R's of radiotherapy, they include *repair* of sublethal damage, *redistribution*, *reoxygenation*, and *repopulation*.[115] Some articles refer to the intrinsic radiosensitivity of a tumor as the fifth "R,"[116] but because at this time radiation oncologists are unable to control this aspect of tumor biology, we will restrict the discussion to that provided above.

Biologic Basis of Dose Fractionation

Cells are able to recover from radiation doses that do not directly cause cell death. As seen in Figure 30.7A, the shoulder region of the radiation survival curve lies at low end of the dose spectrum. The **repair** capacity of cells varies greatly but is consistently greater in normal tissue than in tumor tissues. The clinical implication of delivering dose within the shoulder region of the dose survival curve is that critical normal structures are preferentially spared due, in part, to their ability to repair sublethal damage.

As cells move through the cell cycle, they vary considerably in their radiosensitivity. The first dose of radiation is delivered to an asynchronous cell population and preferentially kills cells in the sensitive phases. Cells that survive the radiation dose are often briefly paused in their cell cycling and ultimately **redistribute** to a new asynchronous population prior to the next radiation dose. Because the redistribution phenomenon primarily affects rapidly proliferating cells, it is negligible in many critical normal tissues and is greater in tumor cells. Thus, redistribution results in a net gain in therapeutic ratio with increasing number of radiation fractions.

Radiation has been shown by a number of groups to result in improved oxygenation of previously hypoxic tumor regions. Because hypoxic cells are more resistant to radiation, **reoxygenation** aids in tumor cell kill. The mechanism of reoxygenation during fractionated radiotherapy remains the focus of significant experimental efforts but appears to involve increased oxygen availability due to removal of tumor cells, lowering of interstitial pressure resulting in improved tumor microcirculation, and normalization of tumor vasculature resulting in improved delivery of oxygenated blood.

Removal of cells by radiation, subtotal surgical resection, or cytotoxic agents in both normal and cancer tissues results in a regenerative response. The time of onset and kinetics of this **repopulation** vary among tissues; in general, rapidly proliferating cells experience early onset of repopulation. Although this response helps reduce normal tissue injury, repopulation of tumors reduces the likelihood of cure. Accelerated repopulation can be overcome by shortening the course of radiotherapy and, as described above, underlies approaches that used 6 fractions per week and twice daily fractionation both of which shorten the overall treatment time. Accelerated repopulation is also thought to underlie the finding that patients with extended treatment times experience worse tumor control rates.

Radiobiology Principles in Clinical Practice

Understanding the “R’s” of radiobiology led to the development of new classes of fractionation schedules. Hyperfractionation delivers two or more small doses of radiation per day while keeping the overall treatment time the same as, or slightly faster than, standard daily fractionation. The use of small fractions increases the tolerance of late-reacting tissues enabling the total dose to be increased by 10% to 15% without worsening late complications.

Accelerated fractionation attempts to deliver similar doses over a shorter treatment time by delivering more than 10 Gy per week. Accelerated fractionation can also be achieved by delivering more than 2 Gy per fraction to the tumor while simultaneously delivering lower doses to at-risk nodal regions. For example, we commonly deliver 70 Gy in 33 fractions of 2.12 Gy to cancers of the head and neck with at-risk nodal regions receiving 60 Gy or 54 Gy in 33 fractions of 1.82 Gy or 1.64 Gy, respectively.

Over the last 25 years, these radiobiologic concepts have been tested in multiple randomized trials of hyperfractionation and accelerated fractionation.[12,117,118] These trials show a consistent 10% to 15% improvement in local control with altered fractionated schedules and little increase in late toxicity. Not surprisingly, they also suggest that acute toxicity (i.e., that related to rapidly proliferating tissues such as the mucosal lining of the oral cavity or skin) is increased by hyper- or accelerated fractionation.

Combination of Radiation with Cytotoxic Agents

Over the years, radiation has been combined with cytotoxic chemotherapeutic agents (e.g., cisplatin, carboplatin, paclitaxel, 5-fluorouracil, mitomycin C, hydroxyurea) to improve organ preservation, local control, and overall survival in head and neck, anal, lung, gynecologic, and brain tumors.[14,119–122] Chemotherapy can be given before (i.e., induction or neoadjuvant therapy), after (i.e., adjuvant therapy), or concurrent with radiation. Over the last few decades, a large number of phase I and II trials have been conducted to test these combinations. To date, only a small fraction of tested regimens have undergone evaluation in randomized clinical trials.[123–126] These studies have been performed based on the premise that compounds that improve the tumor response to radiation more than they do that of normal tissues may increase the therapeutic window (Fig. 30.8), resulting in better patient outcomes (reviewed in Reference 127).

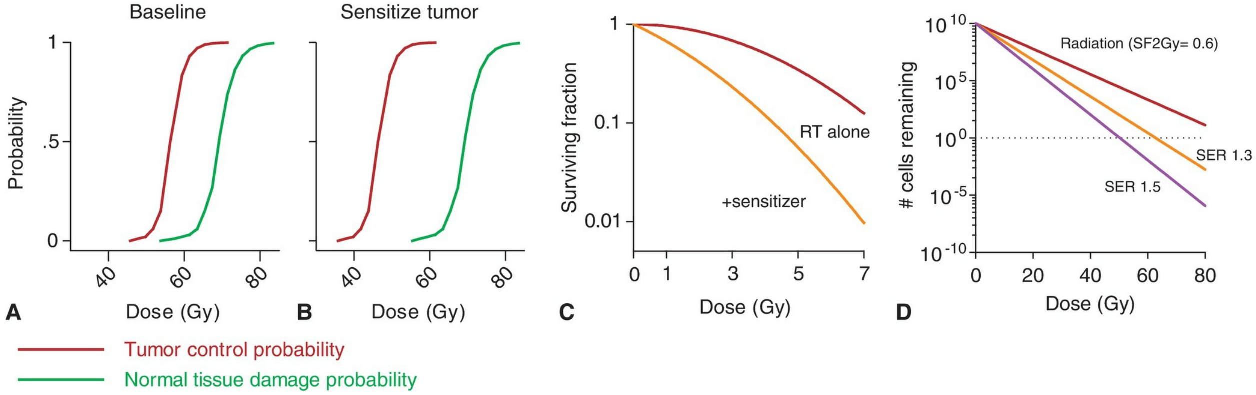

Figure 30.8. Modeling tumor control probability. **A:** The probability of radiation resulting in tumor control (*red*) and normal tissue damage (*green*) can be modeled as sigmoidal dose–response curves. Treatments that sensitize both normal tissue and tumor may shift both curves to the left (not shown). **B:** Treatments that preferentially sensitize the tumor to radiation shift the tumor control curve to the left. **C:** Treatments that sensitize tumor to radiation shift the survival curve left and down (*orange*) compared to radiation alone (*red*). **D:** A palpable tumor may comprise around 10^{10} cells. To cure the tumor, all cells must be removed (<10^{0} cells remaining, *dashed line*). The compounding effect of increased cell kill with the use of a sensitizing agent over 30 or more days of radiation is quite large. In this simplified graphic, a theoretical tumor with 10^{10} cells is treated with multiple 2 Gy daily doses (assume a surviving fraction of 60% per dose) of radiation (*red line*). A treatment that results in 30% greater cell kill each day (SER = 1.3, *orange*) results in theoretical "cure" at around 64 Gy, whereas a 50% increase (SER = 1.5, *purple*) results in "cure" around 52 Gy.

Overall, multiple randomized trials have confirmed a small but defined benefit of concurrent chemoradiotherapy over radiation alone in advanced-stage cancer of the head and neck. Whereas the specifics of these trials are discussed in more detail throughout this book, the sum of these studies favors concurrent therapy for patients with locally advanced cancers in the nasopharynx, larynx, hypopharynx, and oropharynx and for postoperative patients with specific high-risk pathologic features.[18,19]

"Targeted" Combined-Modality Therapy

Although the results of radiation and concurrent cisplatin are encouraging,

there remains substantial room for improvement for most patients with advanced head and neck cancers. Paralleling advances in molecular biology, identification of tumor-specific alterations in normal biologic processes has led to an explosion in targeted therapies. Although a comprehensive review of this rapidly growing field is beyond the scope of this chapter, we will discuss the two best-studied approaches of targeting tumor biology in combination with radiation in head and neck cancer. However, additional studies are underway investigating compounds that target the mitogen-activated protein kinase kinase (MAP2K/MEK/ERK), protein kinase B (PKB; a.k.a., Akt), phosphatidylinositol 3-kinase (PI3K), mammalian target of rapamycin (MTOR), and poly-ADP ribose polymerase (PARP) pathways,[128–132] among others.

In 2006, Bonner and colleagues reported the first trial demonstrating the ability of an antibody-based therapeutic (i.e., cetuximab) to improve outcomes in combination with radiation in locally advanced cancer of the head and neck.[26,27] Cetuximab is a monoclonal antibody that targets the EGFR, a protein that is overexpressed in a large percentage squamous cell carcinomas of the head and neck.[133,134] Upon receptor activation, EGFR initiates a coordinated signaling cascade that regulates cell division, proliferation, differentiation, and cell death. EGFR expression is correlated with poor outcome in patients with head and neck cancer.[34,108,110] In addition, numerous in vitro studies have demonstrated that inhibition of EGFR signaling results in improved tumor control.[135,136] Of particular importance to head and neck cancer, treatment with cetuximab resulted in significantly improved tumor control when given in combination with radiation.[24,137]

Hypoxic Cell Sensitizers

For over 60 years, it has been known that hypoxic tumors are less sensitive to radiation than are well-oxygenated tumors.[138] Worse outcomes in patients with hypoxic tumors appears to be due to both decreased sensitivity to radiation[139,140] and transcriptional changes induced by hypoxia leading to more aggressive tumors.[141–143] As a result of these findings, several studies have investigated the effect of hypoxic modification on outcomes in patients with head and neck cancer.[102,103,144–147] With few exceptions (DAHANCA

study of radiotherapy+/− nimorazole), most of these studies have failed to identify a clinical benefit to hypoxic modification although recent analyses have suggested that the use of a hypoxic modifier results in improved local–regional control in HPV-negative tumors.[102,103] Unfortunately, the lack of direct hypoxia measurements in these studies leaves the absolute benefit of hypoxic modification somewhat ill-defined in the clinical setting.

Intensity-Modulated Radiotherapy

Since its development in the late 1990s, studies have shown that IMRT can effectively limit dose to the salivary glands, mandible, larynx, and pharyngeal constrictors resulting in reduced long-term toxicities and improved patient quality of life as compared to 3-D radiotherapy techniques.[148–150] However, with the exception of cancer of the nasopharynx, cure rates with IMRT appear to be similar to those with older techniques. In the case of cancer of the nasopharynx, as the tumor is often concave in shape and close to many critical normal tissues (e.g., brainstem and optic apparatus), IMRT allows the radiation oncologist to deliver improved dose coverage of the tumor and therefore achieve increased tumor control rates compared to traditional 3-D approaches.[151,152]

Multidisciplinary Care

Cancer care has become increasingly multidisciplinary over the years. Whereas single-modality treatment was historically quite common for many malignancies, this is seldom true today where the majority of cancer patients interface with multiple cancer specialists and treatment modalities to effect a modern treatment package. The multidisciplinary nature of cancer care requires high-quality communication among specialists on behalf of each patient and timely follow-through to ensure that all elements of treatment are efficiently coordinated. The complexity of head and neck cancer care renders this a challenge and the incorporation of tumor boards, case managers, navigators, and routine case reviews can serve a valuable purpose to enhance coordination of care. Once established, the culture of multidisciplinary care becomes second nature and provides great benefit and satisfaction to patients and practitioners alike. No one can master every aspect of care for such a

complex group of cancer patients. Establishing and continually refining (based on evidenced-based review) the multidisciplinary team approach for head and neck cancer patients provides the best opportunity to contend successfully with this challenging disease.

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31 Chemotherapy in the Treatment of Squamous Cell Carcinoma of the Head and Neck

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INTRODUCTION

Cancers of the upper aerodigestive tract comprise a variety of malignancies with different sites of origin extending from the lips to the cervical esophagus, with squamous cell carcinoma (SCC) representing the most prevalent histology. Squamous cell carcinoma of the head and neck (SCCHN) is an aggressive malignancy affecting close to 52,000 patients yearly in the United States and leading to more than 300,000 yearly deaths worldwide.[1] Tobacco smoking and alcohol use are known to be synergistic risk factors in the development of these cancers, which combined, accounted for approximately three-fourths of all SCCHN in the United States in the 1980s.[2] The incidence and prevalence of human papillomavirus (HPV)-associated oropharyngeal cancers have increased in recent years.[3–6] Multiple retrospective series have shown that patients with HPV(+) oropharyngeal squamous cell carcinoma (OPSCC) have a better prognosis than do patients with HPV(−) tumors.[7,8] Recent data suggest that smoking has an adverse effect on prognosis for HPV-positive as well as HPV-negative disease, with the risk of death significantly increasing with each additional pack-year of tobacco smoking.[9] HPV-positive disease also seems to have an unusual metastatic pattern.[10]

Although cancer of the head and neck represents only 5% of all newly diagnosed malignancies in the United States, it remains one of the most challenging to treat. Surgery and radiation therapy are two key components of the initial treatment of locally advanced SCCHN. Based on meta-analysis

data, chemotherapy improves survival in patients treated for cure for nonmetastatic SCCHN with a higher benefit when used concomitantly along with radiotherapy.[11] These trials included patients with cancer of the oral cavity, oropharynx, hypopharynx, and larynx. The role of induction chemotherapy prior to concurrent chemoradiotherapy remains controversial, even though the addition of a taxane to a platinum-based induction regimen has augmented the effectiveness of induction therapy.[12,13] Although this finding has been confirmed by a recent meta-analysis,[14] randomized trials have yet to prove the superiority of adding induction chemotherapy to the standard concurrent therapy approach.[15,16]

Cytotoxic chemotherapy was initially used primarily for palliation in the treatment of cancer of the head and neck. However, its use has gained increased acceptance as a primary and/or adjuvant modality over the past two decades and is now an integral part of the multidisciplinary management of SCCHN. As the objectives of chemotherapy in this field have changed dramatically, systemic therapy has such wide-ranging applications as radiation sensitization and chemoprevention. This chapter reviews the historical usage and current role for chemotherapy in the management of SCCHN.

TREATMENT OF NEWLY DIAGNOSED CANCER—GENERAL APPROACHES

Treatment of SCCHN is complicated by the diversity of cancer sites and origins, the vital anatomic structures within the treated area, and the need for preservation of organ function. The ideal approach to therapy involves a multidisciplinary team of surgeons, radiation and medical oncologists, dieticians, speech pathologists, and dentists. Approximately 30% to 40% of patients with SCCHN present with early-stage cancer manageable with either primary surgery or definitive radiation therapy. In these patients, despite the curative nature of these treatment modalities, the risk of a second primary malignancy is significantly increased compared with the age-matched general population.[17,18] Smoking cessation is of primary importance in reducing the incidence of second primary cancers, and chemoprevention to reduce recurrence rates of index cancers and to prevent the occurrence of second

primary cancers in the aerodigestive tract has been a topic of interest and substantial research effort.[19] Unfortunately, none of the chemopreventive agents studied to date in patients who completed definitive therapy for early-stage disease has shown a clear benefit in prospective randomized clinical trials (please refer to the section of Chemoprevention in this chapter for a more detailed account of this topic).

Even though local therapeutic interventions remain a key component for the treatment of locally advanced SCCHN, chemotherapy has earned a significant role and is now an essential component of managing locally advanced cancer.[20] Treatment planning, including decisions about the use of chemotherapy, should be made within the setting of a multidisciplinary approach. Although functional organ preservation for patients with cancers of the oropharynx, larynx, and hypopharynx has been widely adopted, using nonsurgical approaches in many instances, this still does not apply to oral cavity malignancies where management still relies heavily on surgical resection. Some studies have suggested an added benefit for less extensive surgery when chemotherapy is used for oral cavity cancers, yet this has not been proven in large randomized clinical trials.[21,22]

CONCOMITANT CHEMORADIOTHERAPY

Concurrent chemoradiotherapy significantly decreases the risk of death compared with definitive radiotherapy alone based on the meta-analysis of chemotherapy in cancer of the head and neck (MACH-NC) study, which revealed a 6.5% total decrease in 5-year mortality with the addition of chemotherapy.[11] Although the meta-analysis confirmed a greater benefit with platinum-based chemotherapy, the optimal regimen in the concurrent setting is still a point of debate. High-dose, single-agent cisplatin administered at 100 mg/m^2 on days 1, 22, and 43 in concurrence with conventional single daily fractionated radiation therapy has been considered the standard systemic regimen.[23] However, the improved survival noted with this regimen was also associated with increased toxicities, both acute and chronic.[23,24] It is unclear whether a third cycle of cisplatin would have made a significant difference in outcome. The Radiation Therapy Oncology Group (RTOG) 0129 study

randomized patients to once-daily radiation fractionation with three cycles of cisplatin in comparison to accelerated boost administered over a total of 6 weeks with two cycles only. No significant difference in survival was observed between the two arms. More recent cooperative group trials have restricted cisplatin to two cycles if administered with a concomitant boost approach.

For patients who are not candidates for high-dose cisplatin, a weekly cisplatin regimen has been used with cisplatin doses ranging from 30 to 50 mg/m^2. Although considered to be reasonable options by many, these approaches have not been tested in a randomized prospective fashion in comparison with the every 3 weeks platinum regimen.

Alternative regimens in the case of contraindications to cisplatin include combinations of carboplatin and 5-fluorouracil (5-FU).[25] Taxane-based regimens with the most commonly used weekly paclitaxel and carboplatin have also been considered as acceptable alternatives.[26] Limitations of these approaches have been the lack of agreement on the best taxane schedule and dose and the lack of randomized clinical trials comparing these regimens to cisplatin. A recent meta-analysis comparing the two approaches revealed no clear advantage of cisplatin over the taxane-based regimens that include carboplatin.[27]

Concomitant chemoradiotherapy has been investigated over the past four decades as a primary treatment approach in locally advanced cancer of the head and neck. It is administered with the intent of curing locoregional cancer and controlling the occurrence of distant metastases. Theoretically, systemic control may be feasible if the dose of chemotherapy administered is equivalent to standard systemic doses when given in combination with radiotherapy. Chemotherapy should also act as a radiation sensitizer (by improving the tumoricidal activity of radiation) or as an enhancer (with direct cytotoxic properties against the primary tumor). Therefore, combined chemoradiotherapy provides potentially increased antitumor activity, although often at the risk of substantial local toxicity.

Generally, radiation therapy is administered in two basic schedules: concomitant (simultaneous) or in an interrupted fashion (alternating or split-course schedule). The schedule of radiation delivery may have an impact on both treatment outcome and the incidence of acute and chronic toxicities. A

phase III trial (RTOG 9003) enrolled more than 1,000 patients with locally advanced SCCHN[28] to four arms, including[1] standard radiotherapy,[2] hyperfractionated twice-daily radiotherapy,[3] accelerated fractionated twice-daily therapy, and[4] accelerated fractionated therapy with concomitant boost. After a median follow-up of 23 months, it was determined that hyperfractionated or accelerated radiation therapy with boost provided increased locoregional control and a trend toward improved disease-free survival (DFS) in comparison with conventional radiation therapy. However, no improvement was noted in overall survival (OS). Patients given accelerated split-course fractionation had outcomes similar to those who had received conventional radiotherapy. Clinical investigators continue to incorporate accelerated, fractionated, hyperfractionated, and intensity-modulated radiotherapy (IMRT) approaches in an attempt to maximize tumoricidal activity while minimizing associated toxicities.

Earlier studies examined single-agent chemotherapy with concomitant daily radiotherapy. Cytotoxic agents used in the palliative setting for recurrent or advanced disease have demonstrated single-agent activity when combined with radiation therapy. Frequently administered single agents included cisplatin, methotrexate, 5-FU, bleomycin, ifosfamide, and the taxanes. Several randomized studies have been completed, demonstrating the benefits of combined therapy in comparison with radiation therapy alone. An early randomized trial of radiotherapy alone versus radiotherapy with bolus 5-FU[29] clearly demonstrated superior local control and survival with the addition of 5-FU to radiotherapy in patients with cancer of the oral cavity and oropharynx. Other studies demonstrated the enhanced radiosensitization properties of 5-FU when administered continuously for at least 48 hours following radiation therapy.[30] The continued exposure to 5-FU (via continuous infusion rather than bolus) following radiation therapy seemed to provide superior radiosensitization.[30] On the basis of this principle, a phase I/II pilot study was conducted to study the effects of dose-escalating continuous infusion 5-FU (20 to 30 mg/kg in 5-mg/kg increments) over a 5-day period with four sequential daily fractions of radiotherapy (2.5 Gy) on days 1 to 4, repeated every 14 days.[31] A complete response (CR) rate of 75% was attained in stage IV patients.

In addition, based on preclinical animal models and promising results from earlier studies, hydroxyurea was approved by the FDA for use in

patients with SCCHN when administered concomitantly with radiotherapy.[32] Hydroxyurea has not gained widespread use in concurrence with radiation therapy despite its common use in a few centers such as the University of Chicago. Earlier studies of bleomycin examined its potential synergistic activity in combination with radiotherapy. Two previous randomized studies involving more than 200 patients suggested improved locoregional control in the combined chemoradiation arm.[33] However, the European Organisation for Research and Treatment of Cancer (EORTC) could not confirm benefit of response after completing a randomized study of conventional radiotherapy with or without single-agent bleomycin.[34] Only 64% of patients in the chemoradiation arm received the recommended dose, which may have contributed to the suboptimal response rate and survival time in the combined chemoradiation arm.

The platinum analogues, carboplatin and cisplatin, have a well-defined role in combination with radiation therapy. A large phase III European study evaluated the benefits of concomitant cisplatin (100 mg/m^2, days 1, 22, and 43) with radiation therapy.[35] The study randomly assigned 334 patients to daily radiation therapy or chemoradiotherapy after surgical resection. After a median follow-up of 60 months, the rate of progression-free survival (PFS) was significantly higher in the combined therapy group than in the group given radiotherapy alone (p = 0.04). The OS rate was also significantly higher in the combined therapy group than in the radiotherapy group (p = 0.02), confirming that postoperative concurrent administration of high-dose cisplatin with radiotherapy is more efficacious than is radiotherapy alone in patients with locally advanced cancer of the head and neck and does not cause an undue number of late complications.

Several similar studies have confirmed the advantage of platinum-based concurrent therapy over radiation therapy alone as a definitive therapy for locally advanced SCCHN.[11,36–38] The platinum agent of choice remains cisplatin despite the equivalent results observed in small international trials. Other potential chemosensitizing agents that remain largely investigational include carboplatin and docetaxel.[39,40] The toxicity profile of other agents such as gemcitabine has precluded development in this setting.[41]

Several studies have explored the use of multiagent chemotherapy in concurrence with radiation. Early studies investigated the platinum 5-FU

regimen and revealed encouraging results.[38,42–45] In all, more than 70 randomized trials have compared radiation alone with chemoradiotherapy. Several of these studies involved small cohorts of patients.[11] An example of a study using concurrent cisplatin and 5-FU is the Cleveland Clinic study that enrolled 222 patients with locally advanced SCCHN and administered 96-hour continuous infusion of cisplatin (20 mg/m^2/day) and fluorouracil (1,000 mg/m^2/day) with standard or fractionated radiation.[38] With a median follow-up of 73 months, a 5-year OS rate of 65.7% and a local control rate of 86.7% were observed. The toxicity profile was similar to that of bolus-dose cisplatin with radiation therapy: 78.4% of patients required nutritional support via PEG tube, and one died from a pulmonary embolism.

The MACH-NC meta-analysis, which evaluated a total of 87 trials and 16,485 patients, showed an absolute benefit for chemotherapy of 4.5% at 5 years and a significant interaction ($p < 0.0001$) between chemotherapy timing (adjuvant, induction, or concomitant) and treatment. Both direct (six trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy.[11]

More recently, investigators and cooperative groups have placed increasing focus on the exploration of less intensive regimens with lower end-organ toxicities. This has been accelerated by the finding that HPV status is a strong and independent prognostic factor for survival among patients with cancer of the oropharynx[9] and by the increased incidence of HPV-related oropharyngeal SCC predominantly in Caucasian males.[3,46]

The use of noncisplatin taxane-based regimens in the concurrent setting remains an attractive secondary option for patients who are not candidates for cisplatin therapy, despite the lack of randomized clinical trials in this area. A regimen of weekly carboplatin (100 mg/m^2) and paclitaxel (45 mg/m^2) and concurrent radiotherapy of 70.2 Gy resulted in a CR rate of 75% with a median OS of 33 months that was higher in complete responders with OS rates of 79% and 61% at 2 and 3 years follow-up, respectively.[47] Even though significant acute toxicities were reported, with 70% of patients experiencing grade 3 mucositis, 30% leukopenia, and 25% skin desquamation. However, the ototoxicity and nephrotoxicity typically seen with cisplatin use were not observed. In a second phase II trial, weekly carboplatin with an area under the curve (AUC) of 1 with paclitaxel at 45

mg/m^2 was given with 69.6 Gy of daily radiotherapy to the primary cancer. The primary toxicities included grade 3 or 4 stomatitis, dysphagia, and mucositis in 55% of patients; however, the regimen was effective with an overall response rate (ORR) of 84%, CR rate of 67%, and an OS rate of 60% at a median follow-up of 36 months.[48] Taxane-based regimens remain a very rational approach for patients with contraindications to cisplatin-based therapy. However, no clear randomized trials have established a therapeutically equivalent regimen to the standard cisplatin-based therapy. A recent meta-analysis comparing the two approaches was recently reported[27] and revealed at least equivalent results with the use of taxane-based regimens. The optimal dose and schedule of paclitaxel and carboplatin remain, however, poorly defined.

SEQUENTIAL THERAPY

Induction chemotherapy is administered in a sequential fashion before the provision of definitive surgery and/or radiation therapy. The goal of induction therapy is to assist in both local and distant cancer control. Theoretically, this is done by reducing overall tumor burden before the definitive therapy, which ultimately allows organ preservation and function and possibly improved quality of life. Distantly, the systemic effects of induction chemotherapy may prevent the dissemination of microscopic disease eventually promoting OS. In addition, an improvement in the chance of organ preservation such as preservation of the larynx and hypopharynx is possible, which would have a profound positive impact on quality of life. With the increasing toxicity noted with concurrent therapy schedules, and with the improvement in locoregional control observed with the use of concurrent therapy, interest in curtailing distant metastases as a significant cause of mortality has gained increased importance;[49] hence the concept of sequential therapy, which combines both induction and concurrent therapy approaches. In the MACH meta-analysis, induction chemotherapy offered a meager advantage of 5% improvement in survival over radiation alone; however, this was observed with platinum-based regimens that did not include taxanes.[50,51] Since then, randomized clinical trials comparing induction chemotherapy with cisplatin and 5-FU and a taxane (docetaxel or paclitaxel) showed a clear advantage to adding a taxane in the induction setting and led to the approval of Docetaxel, Cisplatin, 5FU (TPF) as the induction regimen of choice for locally advanced

SCCHN[12,13] (**Table 31.1**).

Table 31.1 Major Randomized Phase III Trials of Induction Chemotherapy in Treating SCCHN

Trial	*N*	Regimens	LRC (2 Years)	OS (2 Years)	PFS (2 Years)
CONCERT (phase II)[99]	150	Panitumumab vs. cisplatin with XRT	51% vs. 61% (NS)	In favor of CRT ($p = 0.03$)	In favor of CRT ($p = 0.10$)
RTOG 0522[100]	895	Cisplatin vs. cisplatin and cetuximab with 70–72 Gy XRT	NA	83% vs. 80% at 2 ($p = 0.17$)	63% vs. 64% ($p = 0.66$)
Bonner trial[101]	213	Cetuximab vs. 70–72 Gy XRT different fractions only	In favor of Cet 41% vs. 50% ($p = 0.005$)	In favor of Cet 45% vs. 55% ($p = 0.03$)	In favor of Cet 37% vs. 46% ($p = 0.006$)
RTOG 1016	742	Cetuximab vs. cisplatin with 70 Gy IMRT (HPV positive only)	Analysis in progress	Analysis in progress	Analysis in progress

In achieving the desired goals of induction chemotherapy, combination treatment with platinum-based 5-FU has been the traditional approach based on its earlier success in recurrent and advanced cancer. Review of the literature suggests that all studies incorporating induction chemotherapy have failed to provide improved locoregional control or a benefit in OS.

Three landmark phase III trials have established the benefits of induction chemotherapy in laryngeal preservation. The Veterans Affairs Laryngeal Study randomly assigned 332 patients with stage III or IV laryngeal carcinoma to receive three cycles of cisplatin/5-FU (PF) followed by conventional radiotherapy or laryngectomy followed by conventional radiotherapy.[52] Response was assessed after the completion of two cycles of chemotherapy. Patients with a partial response (PR) received a third cycle of chemotherapy followed by radiotherapy. In contrast, nonresponders immediately underwent a laryngectomy followed by radiation therapy. An integral component of this study was salvage surgery, which was offered to all patients with residual disease at the completion of radiotherapy. After two cycles of induction, the ORR was 85% (31% CR, 54% PR). Histologic specimens were obtained in 103 patients at the completion of chemotherapy, validating a complete response in 88% of patients with a clinical CR; 45% of those presumed to have a clinical PR were confirmed histologically. Overall, 64% of patients had a histologically confirmed CR. After a median follow-up of 33 months, the estimated 2-year survival was 68% in both treatment groups, and there was no difference in OS ($p = 0.9846$). However, preservation of the larynx was maintained in 64% of patients. Patterns of recurrence differed between the two groups, with increased locoregional

disease failure (p = 0.0005) but decreased metastases (p = 0.016) in the induction chemotherapy group. Although there was no significant difference in OS, this study demonstrates that induction chemotherapy is feasible in the setting of cancer of the larynx, allowing organ preservation without compromising OS. It should be noted that of the 166 patients on the chemotherapy arm, 120 patients (72%) had N0 or N1 disease.

In the RTOG 9111 study, a total of 547 patients with stage III/IV laryngeal carcinoma[53] were randomized to three cycles of induction chemotherapy of cisplatin/5-FU followed by daily radiation therapy, concurrent cisplatin (100 mg/m^2, days 1, 22, and 43) and radiation therapy, or daily radiation therapy only (70 Gy). The primary endpoint was laryngeal preservation rather than OS. A preliminary analysis of laryngectomy-free survival at 2 years showed improvement in both the chemotherapy-containing arms, but notably so in the concurrent chemotherapy arm (58% vs. 66%). Although DFS appeared to be favorable in both chemotherapy arms in comparison with radiation therapy only, no clear difference in OS was noted among the three arms of the study. Time to laryngectomy was superior in the concurrent chemotherapy arm in comparison with the induction arm (p = 0.0094). These recently updated 10-year results continue to show that induction PF followed by RT and concomitant cisplatin/RT shows similar efficacy for the composite endpoint of laryngectomy-free survival. Locoregional control and larynx preservation were significantly improved with concomitant cisplatin/RT compared with the induction arm or RT alone.[53] Hence, it can be concluded that despite variation in methods of treatment, neither has provided an advantage in OS despite the trends favoring induction chemotherapy. Nonetheless, the results from this trial suggest a prolonged DFS and laryngectomy-free interval with the addition of chemotherapy to radiation therapy.

The EORTC verified the benefits of organ preservation in a randomized phase III clinical trial in patients with stage III/IV cancer of the pyriform sinus or aryepiglottic folds.[54] One hundred ninety-four eligible patients were randomly assigned to immediate surgery followed by radiotherapy (94 patients) or induction chemotherapy (100 patients) with cisplatin (100 mg/m^2, day 1) and continuous-infusion 5-FU (1,000 mg/m^2/day, days 1 to 5). An endoscopic examination was completed after each cycle. Patients with a CR or a PR following cycle 2 were offered a third cycle of chemotherapy. Unlike

the Veterans Affairs Laryngeal Cancer Study, patients were required to achieve a CR before undergoing radiation therapy; patients with stable disease were offered salvage surgery followed by radiotherapy. Induction chemotherapy resulted in a CR in 54% of patients at the primary site, and 51% of patients achieved a locoregional CR. Overall, induction chemotherapy provided fewer distant metastases ($p = 0.041$) and an improved median survival (44 months) versus the surgical arm (25 months). Unfortunately, neither arm demonstrated superiority in the prevention of locoregional recurrence. Treatment with induction chemotherapy managed to preserve the larynx in 42% and 35% of patients evaluated for 3- and 5-year estimates of survival. This European study suggests that induction chemotherapy is a feasible alternative if organ preservation is desired without compromising OS. However, it should be noted that only 31% of patients had N2/N3 disease, of which only 6% were N3. Furthermore, patients with N3 disease were eventually excluded from this trial because the first six patients failed to achieve a CR following induction.[54] The updated 10-year results of the EORTC trial 24891 continue to show that more than half of the survivors retain their larynx without compromising survival.[55]

Despite the reduction in distant metastases observed in a number of trials using the induction or sequential approach, the superiority of these approaches over the standard concurrent regimen has yet to be proved in a randomized phase III trial.

Sequential and concurrent therapy were compared head to head in a phase II randomized clinical trial in 101 patients with stage III to IV SCCHN. Patients randomized to concurrent therapy received two cycles of cisplatin plus 5-FU in combination with radiation therapy. Patients assigned to the sequential therapy arm first received three cycles of docetaxel, cisplatin, and 5-FU, followed by the same chemoradiation therapy. The complete radiologic response rate was clearly superior in the sequential arm with an accompanying increase in OS and PFS, providing substantial support to the proponents of induction therapy.[56]

Unfortunately, these results could not be reproduced in two US-based randomized phase III studies comparing the sequential to the concurrent approach (Table 31.1). In the PARADIGM trial, 145 patients were randomized to sequential versus concurrent therapy. The schema of the sequential arm was, however, complicated and was dependent on the

response to induction TPF. Docetaxel was chosen as the concurrent agent of choice with a concomitant boost radiotherapy given to patients with less than good response to induction therapy, whereas standard radiation with concurrent carboplatin was used for the good responders. The trial fell short of completing accrual and accrued <50% of its intended goal. No sign of any benefit from sequential therapy on overall outcome was observed.[15]

The DECIDE trial randomized patients to induction with two cycles of docetaxel, cisplatin, and 5-FU followed by chemoradiotherapy with docetaxel, 5-FU, and hydroxyurea in concurrence with radiation therapy. There was no noted difference in PFS or OS.[16] Febrile neutropenia was also more frequent on the induction arm. Of note is that both of these phase III studies suffered from lack of reaching their accrual targets and an overly pessimistic prediction of outcome for the control arm in the era of HPV-positive OPSCC.

CANCER OF THE NASOPHARYNX

Nasopharyngeal cancer (NPC) is staged according to the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) criteria[57,58] and classified into three subtypes based on the World Health Organization (WHO) criteria: type I or keratinizing, type II or differentiated nonkeratinizing, and type III or undifferentiated, which is usually associated with the EBV virus.[59,60]

It is unclear if systemic therapy in the adjuvant setting or primary therapeutic setting has any value in patients with early-stage NPC given the paucity of clinical trials examining this question. For stage II or intermediate-stage cancer, concurrent therapy is considered a valid approach given the results of a randomized trial favoring the concurrent approach to single-modality radiation therapy. A total of 1,992 patients with stage II NPC were randomized to weekly cisplatin and radiotherapy versus radiation alone. Better OS and PFS were observed on the concurrent therapy arm. In addition, the rate of metastases was more favorable in the concurrent arm.[61]

Concurrent chemoradiotherapy remains the mainstay for the treatment of locally advanced NPC. An early RTOG study opened the door for exploring concurrent modality therapy as the treatment of choice for locally advanced

NPC. In a phase II study comparing concurrent radiotherapy plus cisplatin (100 mg/m^2, days 1, 22, and 42) to standard radiotherapy alone in 124 patients with locally advanced SCCHN,[62] patients with NPC receiving concurrent treatment had an impressive CR of 89% in a subset analysis. Comparison with historically matched controls revealed that DFS and OS were greater in the concomitant arm, thereby revolutionizing the standard treatment of NPC. Subsequently, the large phase III intergroup study 00 to 99 of daily radiotherapy and cisplatin (100 mg/m^2, days 1, 22, and 43) followed by three cycles of adjuvant cisplatin (80 mg/m^2, day 1) and continuous-infusion 5-FU (1,000 mg/m^2, days 1 to 4) every 28 days revealed a clear advantage of the concomitant arm with a 3-year DFS of 69% versus 24% ($p < 0.001$) and a 3-year OS of 78% versus 47% ($p = 0.005$).[63]

Even though the results of the phase III intergroup 00 to 99 study were confirmed in subsequent trials,[64] the acute and late toxicities associated with this regimen have led to the exploration of other effective and less toxic chemotherapeutic combinations. Carboplatin, which is deemed to be less toxic, was compared head to head with cisplatin in this setting with similar efficacy and reportedly lower toxicity. Still, more studies are needed to confirm these preliminary findings.[65]

Given the difficulty in completing the therapeutic regimen on the intergroup 00 to 99 study, an increased interest has developed in sequential therapy for NPC. Patients with stages III and IV disease were randomized to sequential versus concurrent therapy. Although the results were encouraging, the sequential group had a different fractionation schedule for radiation and a higher incidence of toxicities,[66] begging for more studies to investigate this question.

A meta-analysis of six randomized trials evaluating chemoradiation therapy (induction, concomitant, and adjuvant) versus radiation therapy alone verified that the addition of chemotherapy to radiation therapy increased DFS by 37% at 2 years, 40% at 3 years, and 34% at 5 years. The addition of chemotherapy to standard radical radiation therapy for locoregionally advanced cancer of the nasopharynx increases both disease-free/progression-free and OS by 19% to 40% at 2 to 4 years after treatment.[67] In contrast, in a large single-institution study in Hong Kong, 240 patients were randomly assigned to radiation therapy or to two or three cycles of induction

chemotherapy (cisplatin 60 mg/m^2 and epirubicin 110 mg/m^2) followed by radiation therapy.[68] After a median follow-up of 71 months, the investigators determined no statistical benefit with induction chemotherapy in nodal relapse-free survival (p = 0.13), prevention of distant metastases (p = 0.56), or survival (p = 0.55). Despite these results, the addition of chemotherapy is the overwhelmingly accepted standard of care for treating locoregionally advanced NPC.

Systemic therapy is considered the mainstay of care for patients with advanced or recurrent NPC who are not candidates for local therapeutic interventions. In this setting, combination therapies seem to produce superior results when compared to single-agent therapies.[69] Several regimens appear to have equivalent results; however, there is a clear paucity of randomized clinical trials comparing different agents in this setting.[70] EBV DNA levels measured in plasma are reported to predict overall outcome of patients with recurrent metastatic NPC and may be used as a method to assess response and predict outcome.[71] Recently, markers of cisplatin sensitivity such as polymorphism of ERCC1 C8092A were found to be predictors of outcome in cisplatin-treated patients.[72]

Second-line agents for the treatment of refractory disease may include gemcitabine, 5-FU derivatives, the taxanes, topoisomerase I inhibitors, methotrexate, and the vinca alkaloids.[73–76]

POSTOPERATIVE THERAPY

In addition to concurrent or sequential chemoradiotherapy, surgical resection followed by postoperative therapy guided by pathologic findings is considered a standard definitive therapeutic approach in SCCHN. Local and distant recurrences remain frequent after surgery for locally advanced cancer, which presses the need for improved postsurgical adjuvant approaches.[77,78] Radiotherapy in the postoperative setting has been delivered to patients with resected stages III, IVa, and IVb disease with specific indications including surgical margin involvement, perineural and lymphovascular involvement, bone or cartilage invasion, extracapsular lymph node extension, advanced T3 or T4 primary tumors, and N2 or N3 lymph node metastases. This approach has resulted in a 5-year survival rate of close to 30% to 40%.[35,79,80] The

addition of systemic chemotherapy has been shown to improve locoregional as well as overall and disease-free survival in patients with high-risk features.[79,81]

Cisplatin at 100 mg/m^2 added to 60 to 66 Gy of postoperative radiotherapy was tested in trials by both EORTC and RTOG.[35,79] The studies had notable differences in their inclusion criteria as well as their primary objectives, which were locoregional control in the RTOG study and PFS in the EORTC study. Adjuvant concurrent therapy was associated with an improved 5-year PFS (47% vs. 36%, $p = 0.04$) and OS (53% vs. 40%, $p = 0.02$) as well as a lower rate of locoregional recurrence (18% vs. 31%, $p = 0.007$) and a longer time to progression (55 vs. 23 months) on the EORTC trial. This came at a higher toxicity price on the concurrent arm with a significant difference in acute mucositis (41% vs. 21%). On the RTOG study, despite the improved locoregional control and DFS observed in the initial 3-year analysis, the updated 5-year results revealed a loss of significant difference in DFS (37.4% vs. 29.1%, $p = 0.098$) and locoregional control (79.5% vs. 71.3%, $p = 0.086$). It is of note that in both studies, cisplatin did not influence the rate of distant metastases, which were 21% versus 25% in the EORTC study ($p = 0.61$) and 23% versus 21% in the RTOG trial ($p = 0.46$), for the radiation alone arm and concurrent arm, respectively.

To better determine the pathologic characteristics that exerted most of the influence on clinical outcome in these two trials, a more recent pooled analysis of both trials confirmed the importance of microscopically involved surgical margins as well as extracapsular spread of cancer as the most important predictors for the derived benefit in DFS, OS, and locoregional control (23%, 48%, and 30% risk reduction, respectively) when cisplatin was added to radiation.[81]

Cisplatin at the schedule used in both the RTOG and EORTC trials remains the most widely accepted standard of care for patients with high-risk postoperative features. Other smaller trials have scheduled cisplatin on a weekly basis resulting in improvements of 15% in locoregional control ($p = 0.05$), 23% in OS ($p < 0.01$), and 22% in DFS ($p < 0.02$) compared to the nonchemotherapy arm.[82] The role of concurrent adjuvant therapy in patients without high-risk features but with intermediate-risk features including T4 disease, perineural or lymphovascular invasion, N2a or N2b nodal disease, or a surgical margin within 5 mm remains a controversial issue and is currently

being examined by study RTOG 0920. This trial is randomizing intermediate-risk patients to radiation therapy at 60 to 66 Gy only versus the same radiation schedule in concurrence with cetuximab administered at an initial loading dose of 400 mg/m^2 1 week before the start of radiation followed by 250 mg/m^2 weekly during radiation.

Despite the fact that no randomized data exist on the use of taxanes in the postoperative setting, encouraging results from small phase II trials have opened the door for exploring postoperative taxane use in patients with high-risk features. A phase II randomized trial of postoperative radiation with cetuximab combined with either cisplatin or docetaxel (RTOG 0234) revealed a favorable improvement in DFS and OS in the docetaxel arm.[83] This has opened the door for the recently activated RTOG 1216 trial randomizing patients with high-risk features to postoperative radiation delivered with concurrent cisplatin versus docetaxel versus docetaxel and cetuximab.

TARGETING THE EPIDERMAL GROWTH FACTOR INHIBITOR

Overexpression of the epidermal growth factor receptor (EGFR) is recognized in more than 80% of SCCHN.[84] Ligand binding of the extracellular domain results in homodimerization or heterodimerization, causing phosphorylation of the tyrosine kinase domain, leading to cell proliferation and activation. An inverse correlation may also exist between EGFR expression and radioresistance.[85,86] Administration of the chimeric monoclonal antibody against the EGFR cetuximab has been shown to increase radiosensitization, decrease tumor cell line growth, and increase apoptosis (programmed cell death).[87] In vitro and xenograft studies have shown that inhibiting EGFR with cetuximab decreases tumor cell proliferation through the indirect inhibition of its tyrosine kinase activity.[88–91]

Preclinical studies explored the interaction between cetuximab and radiation in human SCCHN cell lines.[92] Cells were treated with cetuximab alone, radiation alone, or cetuximab and radiation. The degree of cell proliferation was markedly inhibited with the combined treatment, regardless

of the degree of EGFR overexpression. When the cell lines were assessed after 48 hours, the extent of apoptosis was greatest in the cetuximab/radiation-treated cell line.

Extensive preclinical and clinical research has led to the approval of cetuximab for the treatment of recurrent metastatic SCCHN. Despite the fact that the ORR with cetuximab in patients with recurrent or metastatic SCCHN does not exceed 13%, a disease control rate of 40% to 46% has been noted.[93,94] Cetuximab was approved as monotherapy for treatment of chemotherapy refractory disease and as a single agent in combination with radiotherapy for treatment of locally advanced SCCHN.

Studies with tyrosine kinase inhibitors of EGFR (EGFR TKIs) resulted in lower responses that did not exceed 10% in small phase II studies.[95,96] EGFR TKIs have also been used in combination with platinum-based systemic therapies with a noted response rate of 21% and a median OS of 7.8 months.[97]

Earlier combinations of cetuximab with radiation led to encouraging results,[98] which set the stage for several larger randomized studies investigating monoclonal antibodies to EGFR in combination with radiation for primary therapy of locally advanced SCCHN (**Table 31.2**). A phase III trial by Bonner et al. in patients with locally advanced SCCHN compared radiation alone to radiotherapy and cetuximab. A total of 213 patients with locally advanced disease received radiation alone and 211 patients received radiation and cetuximab at 400 mg/m^2 loading dose and 250 mg/m^2 subsequent weekly doses. PFS and OS as well as duration of locoregional control were significantly improved with cetuximab despite an equivalent rate of distant metastases on both arms. Patients on the cetuximab versus control arm had a PFS of 17.1 versus 12.4 months (p = 0.006), loco regional control (LRC) of 24.4 versus 14.9 months (p = 0.005), and median OS of 49 versus 29.3 months (p = 0.03), respectively.[101] Updated data continue to show a significant improvement in OS with the addition of cetuximab (45.6% vs. 36.4% at 5 years). Of note however is the lack of information regarding the influence of HPV on response and survival in this study of relatively younger patients with predominantly primary cancers of the oropharynx.[102] A comparison of the toxicity profile revealed no significant differences between the two arms with the exception of the incidence of a rash and infusion

reactions related to cetuximab.

Table 31.2 Major Randomized Phase II/III Trials Using Monoclonal Antibodies to EGFR in Combination with Radiation for Primary Therapy of Locally Advanced SCCHN

Trial	*N*	Regimens	RR	Median OS (Months)	Median PFS (Months)
E5397[106]	117	Cisplatin vs. cisplatin/ cetuximab	10% vs. 26% ($p = 0.03$)	8 vs. 9.2 ($p = 0.21$)	2.7 vs. 4.2 ($p = 0.09$)
EXTREME[107]	442	Platinum based vs. platinum + cetuximab	20% vs. 36% ($p < 0.01$)	7.4 vs. 10.1 ($p = 0.04$)	3.3 vs. 5.6 ($p < 0.001$)
SPECTRUM[108]	657	Cis/5-FU vs. Cis/5-FU + panitumumab	25% vs. 36%	9 vs. 11.1 ($p = 0.14$)	4.6 vs. 5.8 ($p = 0.004$)
ZALUTE[109]	286	Zalutumumab vs. support or methotrexate	6.3% vs. 1.1%	6.7 vs. 5.2 ($p = 0.065$)	9.9 vs. 8.4 ($p = 0.001$)

One of the major criticisms of this study is the choice of radiation alone as the comparator arm, because this is considered a substandard approach at the present. The lack of direct comparison between cisplatin and cetuximab in a randomized phase III trial, in addition to results from retrospective single-institution studies favoring cisplatin, has hindered the adoption of cetuximab and radiation therapy as the standard approach of choice in patients with locally advanced SCCHN. The results of a recently completed phase III study comparing cisplatin with cetuximab (RTOG 1016) are eagerly awaited and may help to resolve this question at least in patients with HPV-positive disease. RTOG 1016 is comparing 5-year OS between cisplatin at 100 mg/m^2 administered every 21 days for 2 doses to cetuximab at 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly in concurrence with 70 Gy IMRT. Local and distant failure rate as well as toxicity and correlative biomarkers will be examined as secondary endpoints.

Given the improvement in outcome observed with the addition of cetuximab to radiotherapy in treating locally advanced cancer, study RTOG 0522 attempted to answer the question of whether the addition of cetuximab to the standard platinum radiation combination would improve PFS for patients with locally advanced disease. The study enrolled a total of 895 evaluable patients, 447 on the cetuximab/cisplatin arm and 448 on the cisplatin only arm. No significant difference in OS was reported in a preliminary analysis presented at American Society of Clinical Oncology (ASCO) in 2011.[100] Additional follow-up is needed to reach the study

endpoints. In the interim analysis, no clear difference in outcome was observed in the subset of HPV-positive patients. In a phase II, randomized trial (CONCERT-2) of the same design using the humanized EGFR monoclonal antibody panitumumab plus radiotherapy compared with chemoradiotherapy in patients with unresected, locally advanced SCCHN, there was a favorable trend for the nonpanitumumab arm for the primary endpoint (locoregional recurrence at 2 years), as well as other measures of efficacy, mostly observed in the HPV-negative population. The relatively small number of patients enrolled compared to RTOG 0522 and the subset analysis limits the conclusions, especially for the HPV-positive group.[99]

At present, no clear standard of care exists in the HPV-positive cancer of the oropharynx (OPCA) patient population. It is clear, however, that HPV-positive OPCA is a distinct clinicopathologic entity with different clinical behavior and improved overall prognosis compared to HPV-negative SCCHN. In an analysis of study RTOG 0129, which examined accelerated-versus standard-fractionation radiation therapy in concurrence with cisplatin, 63.8% of patients with OPCA had HPV-positive status. A significantly improved 3-year OS was observed compared to that in HPV-negative patients (82.4% vs. 57.1%, $p < 0.001$ in HPV-positive vs. HPV-negative OPCA, respectively). Of note is the negative effect of smoking, a higher lymph node metastases, and cancer stage on overall outcome.[9] These findings have opened the door to a newer generation of studies including RTOG 1016, ECOG 1308, and others focusing on HPV-positive OPCA. The standard of care for early, locally advanced as well as metastatic cancer has yet to be defined for HPV-positive disease.

EGFR INHIBITION IN RECURRENT AND METASTATIC SCCHN

Numerous phase II trials have evaluated the activity of cetuximab in the treatment of recurrent or metastatic cancer. Earlier studies enrolled a small number of patients. In one phase II trial, 53 patients with recurrent or metastatic cancer received cetuximab in combination with platinum-based chemotherapy. A response rate of 36% was reported with the most common grade 3/4 toxicities being leukopenia (38%), asthenia (25%), and thrombocytopenia (15%), consistent with the known adverse events noted

with chemotherapy.[103] In a multicenter phase II trial reported by Vermorken et al.,[93] 103 patients with disease progression after platinum-based therapy were treated with cetuximab monotherapy. The response rate did not exceed 13% unfortunately, with a median progression time of 70 days.[93] Hitt et al.[104] reported another phase II study in which cetuximab was combined with weekly paclitaxel at 80 mg/m^2. The ORR in the 42 evaluable patients was 60% with a median PFS of 5.6 months.[104] The regimen was fairly well tolerated. A phase II study reported by Baselga et al.[105] enrolled 96 patients with recurrent metastatic SCCHN who received cetuximab in combination with platinum-based chemotherapy. A response rate of 10% was reported with a disease control rate of 53%. The median PFS time was 85 days with a median OS of 183 days.[105]

Several larger phase III studies have investigated several EGFR monoclonal antibodies in the recurrent metastatic setting (**Table 31.3**). The phase III randomized ECOG 5397 trial enrolled 117 patients who were administered cisplatin with weekly cetuximab or placebo. The median PFS was 2.7 months for the chemotherapy-only arm versus 4.2 months for the cetuximab arm. Despite the lack of difference in OS ($p = 0.21$), the objective response rate favored the cetuximab arm (26% compared to 10%, $p = 0.03$). Skin toxicity manifesting as rash was correlated with improved survival ($p = 0.1$).[106]

Table 31.3 Major Randomized Phase III Trials Using Monoclonal Antibodies to EGFR in Recurrent Metastatic SCCHN

Trial	*N*	Regimens	RR	Median OS (Months)	Median PFS (Months)
E5397[106]	117	Cisplatin vs. cisplatin/cetuximab	10% vs. 26% ($p = 0.03$)	8 vs. 9.2 ($p = 0.21$)	2.7 vs. 4.2 ($p = 0.09$)
EXTREME[107]	442	Platinum based vs. platinum + cetuximab	20% vs. 36% ($p < 0.01$)	7.4 vs. 10.1 ($p = 0.04$)	3.3 vs. 5.6 ($p < 0.001$)
SPECTRUM[108]	657	Cis/5-FU vs. Cis/5-FU + panitumumab	25% vs. 36%	9 vs. 11.1 ($p = 0.14$)	4.6 vs. 5.8 ($p = 0.004$)
ZALUTE[109]	286	Zalutumumab vs. support or methotrexate	6.3% vs. 1.1%	6.7 vs. 5.2 ($p = 0.065$)	9.9 vs. 8.4 ($p = 0.001$)

The phase III EXTREME trial randomized 442 patients with recurrent or metastatic SCCHN to cisplatin or carboplatin plus 5-FU every 3 weeks with or without cetuximab. Close to 39% of patients had received prior systemic therapy prior to randomization as part of first-line therapy. A total of six

cycles of chemotherapy were allowed with cetuximab maintenance continuing until disease progression for patients randomized to the cetuximab arm. Patients on the cetuximab arm had a significantly longer OS compared with those receiving chemotherapy alone (median 10.1 vs. 7.4 months, 95% CI: 0.64 to 0.99). An improvement in PFS (5.6 vs. 3.3 months) as well as response rate (36% vs. 20%) was also noted for the cetuximab arm. EGFR expression did not correlate with skin toxicity from cetuximab.[107] Patients on the cetuximab arm appeared also to have improvements in quality of life measures including symptomatic pain, speech and swallowing, and eating compared to the noncetuximab arm.[110] Unlike HER2 expression in breast cancer, EGFR expression level does not seem to correlate with the chance of responding to cetuximab. In addition, no association between EGFR copy number measured by FISH and overall clinical outcome was noted on this trial.[111]

Other monoclonal antibodies to EGFR have been evaluated in the recurrent metastatic setting. In the SPECTRUM 657 study, patients were randomized to cisplatin plus 5-FU, with or without panitumumab, which is a fully humanized monoclonal IgG2 antibody to EGFR. A nonsignificant trend of improvement in OS was observed on the experimental arm (11.1 vs. 9.0 months, CI: 0.73 to 1.05).[108] Of importance is that patients on the control arm had the option to receive cetuximab off protocol upon disease progression given that cetuximab was approved by that time. This was not the case in the EXTREME trial where patients were not allowed to cross over. Some believe these facts may have contributed to the lack of OS benefit on the SPECTRUM and other trials of similar designs using other EGFR monoclonal antibodies.

In the ZALUTE trial, patients with recurrent and metastatic SCCHN who had failed platinum-based chemotherapy were randomized to receive the EGFR monoclonal antibody zalutumumab versus best supportive care. A total of 286 patients were enrolled. Even though there was a trend favoring OS improvement in the zalutumumab arm, the difference did not reach statistical significance (6.7 vs. 5.2 months, hazard ratio 0.77, 95% CI: 0.57 to 1.05). The disease control rate and PFS rate favored the zalutumumab arm.[109]

THE ROLE OF ANGIOGENESIS AND

VEGF INHIBITION

Angiogenesis is the process by which a cancer develops its own blood supply to promote cell growth and facilitate metastases. Vascular endothelial growth factor (VEGF) is known to increase vascular permeability and promote angiogenesis. Our understanding of the mechanism of angiogenesis has significantly increased over the past two decades resulting in the introduction of antiangiogenic agents as antitumor agents.[77] Elevated VEGF levels have been implicated as a poor prognostic indicator of increased risk of recurrent disease in addition to radioresistance.[112,113] A large number of molecules that are capable of inducing angiogenesis are reportedly released from SCCHN cells. These include, in addition to VEGF, platelet-derived growth factor (PDGF), transforming growth factor alpha and transforming growth factor beta, fibroblast growth factor, and interleukin-8.[114–117] Although most antiangiogenic compounds target VEGF, others target VEGF receptor-2 (VEGFR2) via monoclonal antibodies or small molecule inhibitors or enzymes that degrade the extracellular matrix (matrix metalloproteinases MMPs).[118] TIMP-1 is a natural inhibitor of MMP that also seems to be expressed in SCCHN and may have prognostic value in patients with SCCHN.[119,120] Tumor expression of MMPs may be an important determinant of tumor growth, spread, and clinical outcome.

The recombinant humanized monoclonal antibody against VEGF, bevacizumab, has been one of the most widely investigated antivascular agents in cancer therapy.[117] Multiple phase II and III studies have determined its activity in colon cancer, non–small cell cancer of the lung, and breast cancer.[121,122] Life-threatening pulmonary hemorrhage has been attributed to bevacizumab in patients with cancer of this histology leading to increased caution when using it in patients with this tumors of this histology, including SCCHN.[123] Risk factors that have been identified in patients with cancer of the lung include squamous cell histology and centrally located lesions lying adjacent to major blood vessels.

Conceptually, inhibiting both the extracellular and the intracellular domains of tyrosine kinase may promote further tumoricidal activity. Eventual resistance to EGFR inhibitors has been well established but occurs largely due to an unknown mechanism. Previous in vitro studies have demonstrated up-regulation of VEGF expression through activation of

EGFR.[124] A correlation between resistance to anti-EGFR inhibitors and increased levels of VEGF mRNA in cell lines has been established through in vitro studies.[125] Although VEGF levels were eventually down-regulated in vitro by as much as 50% following administration of an EGFR inhibitor, resistant cell lines continued to demonstrate two- and fourfold increased VEGF levels in comparison with the parent cell line. Hence, combined inhibition of both EGF and VEGF receptors should theoretically result in increased apoptosis, decreased cell proliferation, decreased vascular permeability, and improved cytostatic activity in comparison with the respective single-agent activities.

A phase II randomized clinical trial was recently completed comparing the activity of the combination of cetuximab with sorafenib, which is a multityrosine kinase as well as VEGF inhibitor, with cetuximab alone in patients with recurrent and metastatic disease. The results of this study are still being analyzed. ECOG 1305 is another phase III randomized clinical trial addressing the value of adding bevacizumab to chemotherapy in patients with recurrent metastatic SCCHN. The trial is expected to complete accrual in the summer of 2014.

In summary, even though preclinical data do exist to support the role of angiogenesis and its inhibitors in SCCHN, the use of antiangiogenic agents in SCCHN should also be considered within the context of a clinical trial.

CHEMOPREVENTION

The well-described multistep carcinogenesis process in upper aerodigestive tract malignancies and the predilection for developing cancers throughout the mucosa of the upper aerodigestive tract (field cancerization) in patients with known SCCHN provide the rationale for pharmacologic intervention in patients with known premalignant lesions or patients at risk for developing second primary cancers.[19,126–128] One of the goals of chemoprevention is to decrease the chance of developing other primary cancers, which requires large randomized clinical trials.

Early trials of chemoprevention have focused on vitamin A derivatives. One of the early trials utilized vitamin A (300,000 IU) and beta carotene (360 mg) once a week versus placebo for a duration of 12 months. The rate of complete remission of oral precancerous lesions was improved with either

agent over the placebo arm (52%, 33%, and 10%) for the vitamin A, beta carotene, and placebo arms, respectively.[129] Other trials focusing on primary prevention using vitamin E (alpha-tocopherol) and beta carotene as single agents or in combination have failed to show a benefit over placebo.[130,131] The same agents have been tested in a large double-blind, placebo-controlled, randomized chemoprevention trial enrolling 540 patients with stage I or II cancer of the head and neck with the aim of reducing the risk of second primary cancers. Surprisingly, compared with patients receiving placebo, patients receiving alpha-tocopherol supplements had a higher rate of second primary cancers during the supplementation period (HR = 2.88, 95% CI: 1.56 to 5.31) that declined after discontinuation of the supplement (HR = 0.41, 95% CI: 0.16 to 1.03).[132]

The utility of synthetic retinoids, isotretinoin (13-cis-retinoic acid), all-trans-retinoic acid, and etretinate was extensively studied in chemoprevention studies. In a large randomized European trial, a 2-year supplementation of retinyl palmitate and/or *N*-acetylcysteine resulted in no benefit in terms of survival, event-free survival, or second primary cancers for patients with cancer of the head and neck or with cancer of the lung, most of whom were previous or current smokers.[133,134] In a pivotal randomized placebo-controlled clinical trial, 44 patients with documented oral leukoplakia were randomized to 13-cis-retinoic versus placebo for 3 months and followed for 6 months. There were major decreases in the size of the lesions in the intervention group versus placebo (p = 0.0002), and dysplasia was significantly reversed (p = 0.01). However, over 50% of responders relapsed within 3 months of treatment cessation, and the observed toxicity precluded the development of this approach in larger trials.[135] A subsequent study with low-dose isotretinoin showed more activity against leukoplakia than with beta carotene and that it was better tolerated.[136] In a subsequent large randomized phase III trial of low-dose isotretinoin for prevention of second primary cancers in patients with stage I and II cancer of the head and neck, low-dose isotretinoin was not effective in reducing the rate of second primary cancers or death or smoking-related disease. Smoking statistically significantly increased the rate of second primary cancers and death.[137] Other approaches have focused on biochemopreventive therapy using high-dose isotretinoin, alpha-tocopherol, and interferon alpha and have produced encouraging results; however, these could not be tested in a large cooperative

group trial in light of poor accrual.[138,139] Overcoming resistance to retinoids and minimizing toxicity have been the focus of the newer generation of receptor-selective, synthetic retinoids.[140]

The high rate of EGFR expression in SCCHN has raised interest in targeting this receptor in a newer generation of SCCHN chemoprevention studies.[141–143] Given their route and relative ease of administration, the EGFR TKIs were preferred over monoclonal antibodies to target premalignant lesions.[144,145]

A large spectrum of preclinical and clinical studies has suggested that inhibition of cyclooxygenase-2 (COX-2) enzyme may provide a therapeutic and possibly preventive value for different malignancies including SCCHN.[146–153] The gradual increase in the different grades of dysplasia up to invasive SCCHN supports the use of these agents in subjects with premalignant lesions of the head and neck.[154,155] Consequently, a number of clinical trials have been launched using COX-2 inhibitors as chemopreventive agents for SCCHN.[156] Studies using COX-2I as a single agent in oral premalignant lesions revealed evidence of improvement in the degree of dysplasia.[157]

As evidence also exists of an interaction between EGFR and COX-2 pathways, targeting these two pathways simultaneously has been evaluated in preclinical and clinical studies.[154,158,159] Clinical trials using a combination of EGFR and COX-2 inhibitors in patients with premalignant lesions have revealed a correlation between biomarker modulation and reversal of dysplasia.[160,161] The toxicities observed using these combinations have precluded the possibility of dose escalation or the use of these combinations in larger phase II or III trials in this patient population of healthy subjects.[160] There is an increased interest in exploring natural compounds as chemopreventive agents in light of their low toxicity profile and the higher likelihood to have a higher benefit-to-risk ratio in combination studies.[162]

COMMON CYTOTOXIC AGENTS USED IN TREATING SCCHN

Cisplatin

Review of the literature identifies cisplatin as the only chemotherapy agent evaluated in a randomized phase III trial in comparison with best supportive care; historically, it provided an extension in OS of ~10 weeks.[163,164] Standard regimens have evaluated cisplatin 100 mg/m^2 every 21 to 28 days.[164] However, systemic treatment with cisplatin may be difficult to tolerate, with potential adverse reactions of emesis, electrolyte disturbance, nephrotoxicity, peripheral neuropathy, and ototoxicity. There is an interest in exploring weekly regimens of cisplatin in concurrence with radiation therapy. Cisplatin remains an essential chemotherapeutic agent in the treatment of locally advanced as well as recurrent or metastatic cancer.

Carboplatin

The platinum analogue carboplatin is associated with reduced nephrotoxicity and emetogenicity but is infrequently used as a palliative single agent.[165] Carboplatin has been extensively examined in combination regimens. It is rarely used as a single agent in combination with radiation therapy or in recurrent or metastatic disease and is usually combined with a taxane in the concurrent setting.[166]

Methotrexate

Methotrexate is an antifolate that was initially considered the standard for palliative treatment owing to its ease of administration and moderate associated toxicities. Methotrexate provided variable response rates ranging from 10% to 40% with a short median duration of response as a single agent.[163,167–169] Several characteristics of methotrexate qualify it as an ideal palliative agent. It is currently used mostly in refractory recurrent metastatic cancer as a form of palliation. Methotrexate is not recommended in the concurrent setting.

Ifosfamide

The efficacy of ifosfamide has been investigated in the palliative care setting. Ifosfamide is a synthetic analogue of cyclophosphamide. Diversified schedules have been attempted when ifosfamide is used, with variable

response rates.[168,170–172] Ifosfamide is rarely used in the recurrent or metastatic setting or in the induction setting.

5-Fluorouracil

5-FU is given primarily by continuous infusion for 4 to 5 days every 3 weeks.[164,173] A single-institution retrospective analysis observed a response rate of 31% with bolus infusion of 5-FU.[174] Primary toxicities that have been encountered with 5-FU on both continuous infusion and bolus schedules are palmar–plantar erythrodysesthesia (hand–foot syndrome), mucositis, myelosuppression, and diarrhea. It is a component of the standard induction regimen (TPF) and also a component of the combination of carboplatin/5-FU used in the recurrent metastatic setting in combination with cetuximab in patients who cannot tolerate cisplatin.[12,13,15]

Paclitaxel and Docetaxel

Members of the taxoid class, paclitaxel (Taxol) and docetaxel (Taxotere), have a distinct mechanism. Paclitaxel functions to promote the assembly of microtubules from tubulin dimers and to stabilize microtubules by preventing depolymerization, resulting in mitotic arrest at the G2/M phase and subsequent apoptosis (programmed cell death).[175] This cytotoxic agent was originally discovered in 1971 and is derived from the Pacific yew tree, *Taxus baccata*. Paclitaxel is formulated in Cremophor (polyoxyethylated castor oil), resulting in severe hypersensitivity reactions in 2% to 4% of patients. Additional adverse events that have been reported include urticaria, angioedema, dyspnea, hypotension, and anaphylaxis. All patients require premedication with corticosteroids, diphenhydramine, and H_2-antagonists to prevent adverse reactions.

A variety of infusion schedules have been evaluated to determine the optimal method of administering paclitaxel without compromising efficacy.[176–178] Paclitaxel continues to be evaluated in both single-agent and combination chemotherapy treatment regimens. Response rates have varied from 20% to 40% in the recurrent or metastatic disease setting. Peripheral neuropathy and myelosuppression are the primary treatment-limiting toxicities. Paclitaxel is often used in combination with platinum in the recurrent or metastatic setting as well as in concurrence with radiation

therapy for locally advanced cancers. Markers of taxane sensitivity such as acetylated tubulin or beta-tubulin have been suggested as possible predictors of response to these agents in SCCHN.[179,180]

The semisynthetic taxane, docetaxel, has a mechanism of action similar to that of paclitaxel in promoting microtubule stabilization. Unlike paclitaxel, however, docetaxel does not alter the number of protofilaments in the bound microtubules, and it prevents formation of the centrosome rather than affecting the mitotic spindle. Docetaxel is now an integral part of the approved induction regimen of TPF and is often used in the recurrent metastatic setting as well.[12,14,15]

Traditional schedules of docetaxel in the treatment of cancer of the head and neck have been administered at 100 mg/m^2 every 21 days with response rates of 20% to 40%. Docetaxel was determined to be active and safe, with an ORR in one study of 42%.[181] A similar French study provided an ORR of 20.8%.[182] These two studies differ in their patient populations, with the majority of patients in the French study (73.9%) having metastatic disease. Principal toxicities of docetaxel include leukopenia, asthenia, peripheral edema, peripheral neuropathy, and hypersensitivity reactions. Docetaxel continues to be evaluated in palliative, induction, and concurrent radiation treatment settings.[12,13,15]

Hydroxyurea

Hydroxyurea is an oral agent that inhibits ribonucleotide diphosphate reductase, which interferes with DNA synthesis, specifically disrupting the S-phase of the cell cycle.[183] In preclinical animal models, hydroxyurea may prevent cells from moving from the G1-radiosensitive phase to the radioresistant phase.[184] It has been FDA approved for use in combination with radiation therapy in SCCHN based on results from earlier studies[32] and has been more recently used in concurrence with radiation in a large randomized trial of induction with two cycles of docetaxel, cisplatin, and 5-FU followed by chemoradiotherapy with docetaxel, 5-FU, and hydroxyurea—the DECIDE trial.[16] The use of hydroxyurea in SCCHN remains however limited to few centers and has not gained widespread use.

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32 Cancer of the Head and Neck: Targeted Molecular Therapy of Head and Neck Cancer

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INTRODUCTION

Significant progress has been made in understanding the molecular biology of squamous cell carcinoma of the head and neck (SCCHN) including large-scale comprehensive sequencing, mutational analysis, and transcriptome arrays. From these analyses, it has become clear that several actionable alterations occur in SCCHN and that distinct biologic subtypes exist that depend on different biologic processes. The two broadest subtypes of SCCHN can be divided generally by etiology into tobacco related and human papillomavirus (HPV) related. It is clear that these subtypes not only represent entities that behave differently clinically but are quite disparate in their molecular phenotype and presumably in their sensitivity to specific targeted agents. This chapter will review the development of the most commonly tested targeted agents in SCCHN with an emphasis on drugs that have at least reached clinical trials. The only approved molecularly targeted agent in SCCHN currently is cetuximab, but as the number of agents grows and our ability to use predictive biomarkers improves, it is likely that many more will become part of standards of care in the near future.

Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) is a transmembrane cell

surface receptor that is a member of the ErbB family of receptor tyrosine kinases. The EGFR is activated by ligand binding that results in receptor homodimerization and stimulation of intracellular protein tyrosine kinase activity and activation of downstream signaling pathways including PI3K/AKT and RAS/MAPK/ERK. Dysregulation of the EGFR by increased expression or mutations can lead to altered growth signals and tumorigenesis.

The discovery that the EGFR is highly expressed in SCCHN marked the beginning of the era of targeted therapy for the treatment of SCCHN. The EGFR is expressed in the majority of patients with SCCHN and is associated with poor prognosis.[1–7] In a landmark paper by Grandis et al.,[2] it was demonstrated that mRNA from both the ligand TGF-α and the EGFR were significantly elevated in both tumor specimens and histologically normal mucosa specimens from patients with SCCHN compared with tissue from normal control patients. Ang and colleagues retrospectively tested tissue from 155 patients with SCCHN enrolled in a phase III trial for EGFR overexpression and correlated the results with multiple variables including T and N stage and survival endpoints. There was no association between high EGFR expression and T or N stage or the rate of distant metastases. However, both overall survival and disease-free survival rates of patients with high EGFR-expressing SCCHN were significantly lower (p = 0.0006 and p = 0.0016, respectively), and the local–regional relapse rate was significantly higher (p = 0.0031) compared with those of patients with low EGFR-expressing SCCHN.[4]

The strong preclinical evidence for the role of EGFR signaling in the genesis and progression of SCCHN led to the development of drugs targeting the EGFR that have met with mixed success in the clinical arena. Both monoclonal antibodies and small molecule tyrosine kinase inhibitors (TKIs) have been studied in clinical trials, but to date, only the EGFR monoclonal antibodies have achieved routine use in clinical practice.

EGFR Monoclonal Antibody: Cetuximab

Cetuximab (Erbitux, Bristol-Meyers Squibb, Princeton, NJ) is a chimeric monoclonal antibody that was first approved by the FDA in 2006 for use in patients with locally advanced cancer of the head and neck in combination with radiation therapy, thus making it the first approved targeted therapy for SCCHN. The standard dosing for cetuximab is an initial loading dose of 400

mg/m^2 followed by weekly doses of 250 mg/m^2. The long half-life of cetuximab does allow for every other week dosing with similar efficacy.[8] The classic side effect of cetuximab is an acneiform rash, present in 76% to 88% of patients, with 1% to 17% having a severe rash.[9] Other skin toxicities are commonly seen including skin dryness and fissuring, paronychia, and secondary bacterial skin infections. Infusion reactions are also common with cetuximab and can be serious (even fatal) in ~3% of patients overall. However, the rate of infusion reactions can vary by geographic region, with consistently higher rates (up to 25%) reported in the southeastern United States.[10–13] Cardiopulmonary arrest and sudden death have been reported in 2% of patients receiving cetuximab concurrent with radiation therapy and 3% of patients receiving cetuximab in combination with cytotoxic chemotherapy. Close monitoring of serum electrolytes, including magnesium, is strongly recommended.[9]

Cetuximab has been approved for use in SCCHN as part of definitive treatment in combination with radiation therapy, for R/M-SCCHN in combination with platinum-based cytotoxic chemotherapy, and as a single-agent for R/M-SCCHN after progression on platinum-based therapy. The subsequent pages will describe the key clinical trials that led to these approved indications.

Cetuximab with Radiation therapy for Locally Advanced SCCHN

In 2006, Bonner et al.[14] published a landmark trial in the New England Journal of Medicine that showed the benefit of cetuximab when added to definitive radiation therapy for the treatment of locally advanced SCCHN (LA-SCCHN). In this phase III, multinational, randomized study, 213 patients with LA-SCCHN were treated with radiation therapy and 211 patients were treated with radiation therapy plus weekly cetuximab (initial dose 400 mg/m^2 followed by 250 mg/m^2 weekly for the duration of radiation therapy). Baseline patient characteristics were well balanced. The majority of patients in both arms had cancer of the oropharynx followed by cancer of the larynx and hypopharynx; patients with cancer of the oral cavity were not included. Approximately 30% of the primary cancers in each arm were T4. Treatment toxicities were similar in both arms with the exception of

increased grade 3 or 4 rash and infusion reactions in the patients receiving cetuximab. With a median follow-up of 54 months, the addition of cetuximab to definitive radiation therapy significantly improved survival outcomes. In patients treated with cetuximab and radiation therapy, the median duration of locoregional control was 24.4 months compared with 14.9 months in patients treated with radiation therapy alone (HR for locoregional progression or death, 0.68, p = 0.005). The median 3-year overall survival for patients treated with cetuximab plus radiation therapy was 49.0 months compared with 29.3 months in patients treated with radiation therapy alone (HR for death, 0.74, p = 0.03). The addition of cetuximab to radiation therapy significantly prolonged 3-year progression-free survival from 12.4 to 17.1 months (HR 0.70, p = 0.006). Long-term follow-up results of this landmark trial reported persistent survival benefit at 5 years in patients who received cetuximab and suggested a benefit in those patients who developed a rash greater than or equal to grade 2.[15] The Bonner trial established concurrent cetuximab and radiation therapy as a curative treatment option for LA-SCCHN, although the standard of care for most patients remains concurrent radiation therapy and cisplatin. The fact that the control arm in the Bonner trial was radiation therapy alone, which is no longer considered standard of care for patients with LA-SCCHN with a good performance status, makes it difficult to interpret the results in light of other, more established treatment options. The TREMPLIN study for larynx preservation randomized 116 patients who responded to induction chemotherapy to either chemoradiation with high-dose cisplatin or radiation therapy with cetuximab, but could not prove one regimen to be superior to the other.[16] To date, there are no completed phase III trials that definitively show that cetuximab with radiation therapy is superior to chemoradiation therapy for LA-SCCHN.

Based on the premises that cetuximab added to chemotherapy enhances the response rate and improves survival in patients with R/M-SCCHN and that cetuximab is a radiation sensitizer, the randomized, phase III trial by the Radiation Therapy Oncology Group (RTOG) 0522 was conducted to assess the incremental benefit of adding cetuximab in the curative treatment setting to a backbone of accelerated radiation therapy (72 Gy in 42 fractions over 6 weeks) and two cycles of high-dose cisplatin (100 mg/m^2).[17] From November 2005 through May 2009, 941 patients with stage III or IV SCCHN were enrolled and 891 analyzed. Most of the patients were men (88%) with cancer

of the oropharynx (70%; 73% p16 positive). Although the results were much anticipated, the addition of cetuximab failed to improve any outcome measures but did increase overall treatment toxicity. Patients with p16-positive cancer of the oropharynx had improved overall survival compared with p16-negative patients (85.6% vs. 60.1%, $p < 0.001$), as expected. EGFR expression did not determine survival outcomes. The combination of concurrent radiation therapy, cisplatin, and cetuximab as curative-intent therapy should not be routinely used unless specific subsets of patients who may benefit can be identified.[17]

Cetuximab for Recurrent/Metastatic SCCHN

Multiple studies have investigated the use of cetuximab for recurrent/metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN) both as a single agent and in conjunction with cytotoxic chemotherapy. In 2005, two phase II trials that examined the role of cetuximab in patients with platinum-refractory R/M-SCCHN were published in the *Journal of Clinical Oncology*.[18,19] One trial by Herbst and colleagues treated 132 patients with squamous cell carcinoma of the oral cavity, pharynx, and larynx with a platinum doublet (cisplatin/paclitaxel or cisplatin/5-fluorouracil) to assess for responsiveness to platinum therapy. The 30 patients who responded to the initial chemotherapy were continued on the same regimen. The remaining patients with either stable disease ($n = 51$) or disease progression ($n = 25$) were subsequently treated with cisplatin (75 to 100 mg/m^2 once every 3 weeks) plus cetuximab at standard doses. A protocol amendment was performed after trial initiation to allow treatment of patients with progressive disease within 90 days of initial response to the platinum regimen with cisplatin and cetuximab ($n = 54$). Cetuximab did have activity in patients with proven platinum-refractory disease. In the group of patients with immediate progression or stable disease on platinum therapy, 20% and 18%, respectively, of patients subsequently responded to platinum and cetuximab. In contrast, only 6% of the patients who initially responded to platinum therapy but progressed within 90 days achieved a response upon treatment with cisplatin and cetuximab. Median durations of response for patients with immediate progression on platinum therapy, with progression within 90 days of platinum therapy, and with stable disease were 4.2, 4.1, and 7.4 months, respectively, with corresponding median overall survivals of 6.1,

4.3, and 11.7 months in patients who received cisplatin with cetuximab.[18] Although the response rate to cisplatin/cetuximab in patients with initial progressive disease and those with stable disease were similar, the median response rate and overall survival were much better in the patients with stable disease, likely speaking to a more favorable underlying biology in this group of patients. Nonetheless, this trial was proof of principle that platinum resistance could be overcome with the addition of cetuximab in a subset of patients with R/M-SCCHN, albeit short-lived. The second trial by Baselga et al.[19] enrolled patients with R/M-SCCHN with documented disease progression on a regimen of cisplatin or carboplatin. Ninety-six patients who met eligibility criteria were treated with platinum therapy at the same doses on which they progressed along with cetuximab at standard doses. The response rate was 10%, and the disease control rate (all responses plus stable disease) was 53%. Median time to progression was 85 days, and median overall survival was 183 days.

The single-agent response to cetuximab in patients with R/M-SCCHN after failure of platinum-based chemotherapy was shown to be 13% in an open-label, multicenter phase II trial by Vermorken et al.[20] The study design allowed patients who progressed on cetuximab alone to subsequently receive salvage therapy with platinum and cetuximab. In the initial phase, 103 patients with platinum-refractory disease were treated with cetuximab at standard doses with a response rate of 13%, disease control rate of 46%, and median time to progression 70 days. Of the 53 patients who progressed on cetuximab and went on to receive salvage therapy, there were no responders. This trial highlights the very modest benefit of single-agent cetuximab and underscores the need for a reliable biomarker for patients who will respond to cetuximab, so as to avoid unnecessary toxicity and treatment cost in those patients unlikely to derive a benefit from this therapeutic approach. Given the similar response rates of the trials by Baselga and Vermorken in platinum-refractory disease (10% and 13%, respectively), there does not appear to be any benefit of retreating patients with platinum-refractory R/M-SCCHN with a platinum agent, as a similar response could likely be achieved with cetuximab alone with less toxicity.

In 2006, Burtness and colleagues reported in the Journal of Clinical Oncology that the addition of cetuximab to cisplatin in patients with R/M-SCCHN improved overall response rate but not progression-free or overall

survival. In this phase III, randomized, placebo-controlled trial, 117 patients with R/M-SCCHN were randomized to receive cisplatin 100 mg/m^2 IV once every 4 weeks with cetuximab (Arm A) or placebo (Arm B). The study was negative for its primary endpoint of progression-free survival (4.2 months with cetuximab, 2.7 months with placebo; p = 0.09). Median overall survival was 9.2 months with cetuximab and 8.0 months with placebo (p = 0.21). The objective response rate was significantly improved with the addition of cetuximab from 10% with placebo to 26% (p = 0.03).[21]

The EXTREME trial by Vermorken et al.[22] in 2008 that added cetuximab to a regimen of platinum and 5-fluorouracil was the first trial to demonstrate an improvement in overall survival in patients with recurrent/metastatic cancer since the introduction of cisplatin in the 1980s.[23] The study was a first-line therapy trial for patients with R/M-SCCHN and randomized 220 of 442 eligible patients to platinum (cisplatin 100 mg/m^2 IV or carboplatin [AUC 5] on day 1) and 5-fluorouracil (1,000 mg/m^2/day days 1 to 4) with or without cetuximab at standard doses for a maximum of six cycles. In patients with a response of stable disease or better, cetuximab was continued until disease progression or unacceptable toxicities. The addition of cetuximab to cytotoxic chemotherapy improved the median overall survival from 7.4 to 10.1 months (HR 0.80, p = 0.04). Both progression-free survival and response rate were also significantly improved in the cetuximab arm. Sepsis was significantly more common in the patients who received cetuximab (p = 0.02), but no cetuximab-associated deaths were reported. A separate quality of life (QOL) analysis reported that the addition of cetuximab to chemotherapy did not adversely affect patient QOL.[24] Although the EXTREME trial to date represents the regimen with the longest median overall survival in patients with recurrent/metastatic cancer, it is not known whether first-line platinum-based chemotherapy followed by second-line cetuximab could achieve the same survival benefit. Given the overall survival benefit and lack of measurable effect on QOL, it is a very appropriate regimen to consider for patients with R/M-SCCHN who have a good performance status for whom aggressive therapy is appropriate.

Although most of the studies of cetuximab in combination with chemotherapy in patients with R/M-SCCHN have included platinum-containing regimens, one promising phase II trial studied the combination of weekly cetuximab at standard doses with paclitaxel (80 mg/m^2 weekly) as

first-line treatment for patients with R/M-SCCHN.[25] Treatment was well tolerated, and the overall response rate was 54% (95% confidence interval [CI] 39% to 69%), with 10 (22%) complete responses and a disease control rate of 80%. Median progression-free and overall survival times were 4.2 (95% CI 2.9 to 5.5 months) and 8.1 months (95% CI 6.6 to 9.6 months), respectively.[25] This regimen represents a good therapeutic option, particularly for patients who develop recurrent/metastatic disease shortly after completing definitive chemoradiation therapy with a platinum agent, or for those patients whose performance status precludes the use of platinum chemotherapy.

Lack of Predictive Biomarkers for Benefit of EGFR Monoclonal Antibodies

Despite the fact that the majority of SCCHN overexpress EGFR, only a fraction of patients will have a major response to treatment with EGFR inhibitors.[20] To date, there is no reliable biomarker that can predict response or primary resistance to EGFR inhibition in SCCHN. Multiple secondary analyses of the EXTREME trial have been conducted to try to identify a predictive biomarker for response to cetuximab, including analyses of EGFR copy number, tumor EGFR expression, and p16/HPV status. Licitra et al.[26,27] performed sequential analyses of the tissue of patients treated on the EXTREME trial to explore whether EGFR copy number or EGFR expression were candidate predictive biomarkers for efficacy of cetuximab in the first-line recurrent/metastatic setting in combination with platinum-based chemotherapy. In 2011, the investigators used dual-color fluorescent in situ hybridization (FISH) techniques to determine the absolute and relative EGFR copy number in 312 of 442 (71%) patient samples. Only 11% of tumors were found to have a high level of amplification of the EGFR gene; most tumor samples were modestly amplified. There was no association of EGFR copy number with overall survival, progression-free survival, or best overall response. The authors concluded that EGFR copy number was not a candidate predictive biomarker for response to cetuximab in combination with first-line platinum/5-fluorouracil chemotherapy in patients with R/M-SCCHN.[26] In 2013, the same investigators published a similar analysis exploring whether tumor EGFR expression level was predictive of cetuximab benefit. Tissue was available from 93% of patients treated on the EXTREME

study, and tumor EGFR expression level was scored (scale 1 to 300). The benefit of adding cetuximab to chemotherapy was seen across all score ranges, indicating that tumor EGFR expression was not a valid predictive biomarker.[27]

In 2014, a retrospective analysis of the EXTREME trial was conducted to see if there was a differential response to cetuximab and first-line platinum chemotherapy by p16 and HPV status.[28] Paired tissue samples were used to assess p16INK4A expression and HPV status in extracted DNA samples using oligonucleotide hybridization assays. A total of 416 (of 442) patients had available tissue. Only 10% of tissue was positive for p16 and 5% for HPV; these patients had improved survival compared with patients who were p16 or HPV negative. HPV or p16 status did not appear to influence response to therapy; cetuximab combined with chemotherapy improved outcomes in both groups.[28] In contrast, p16 subset analysis of the SPECTRUM trial (chemotherapy with or without panitumumab in patients with R/M-SCCHN, see section “Other EGFR Monoclonal Antibodies”) suggested a possible increased benefit of EGFR inhibition in patients with p16-negative tumors. In 443 (67%) patients, p16 status was assessed and 99 samples (22%) were p16 positive. Median overall survival in patients with p16-negative tumors was longer in the panitumumab group than in the control group (11.7 months [95% CI 9.7 to 13.7] vs. 8.6 months [6.9 to 11.1]; HR 0.73 [95% CI 0.58 to 0.93]; p = 0.0115), but this difference was not shown for p16-positive patients (11.0 months [7.3 to 12.9] vs. 12.6 months [7.7 to 17.4]; 1.00 [0.62 to 1.61]; p = 0.998).[29] Further studies are needed to validate or refute these findings.

Cetuximab as a Component of Induction or Adjuvant Therapy

Induction chemotherapy followed by definitive chemoradiation is an acceptable treatment paradigm for LA-SCCHN. The accepted standard induction therapy regimen is cisplatin (75 to 100 mg/m^2 day 1), docetaxel (75 mg/m^2 day 1), and 5-fluorouracil (1,000 mg/m^2 days 1 to 4) once every 21 days for three cycles followed by definitive chemoradiation.[30,31] Cetuximab as part of induction chemotherapy was initially studied in a phase I trial and found to be safe and tolerable.[32] Two phase II studies added cetuximab to

carboplatin and paclitaxel in both the induction and definitive chemoradiation component of treatment. The regimen was felt to be safe and effective.[33,34] However, the Brown study compared their results to prior studies that had been conducted at their institution using the same regimens without cetuximab, and the survival results appeared the same.[35,36] The future of induction therapy with or without cetuximab remains to be determined.[37]

The role of cetuximab as part of adjuvant therapy for resected SCCHN is still under investigation. The randomized phase II trial conducted by the RTOG 0234 randomized patients with resected stage III or IV SCCHN with one or more risk factors including extracapsular extension, positive surgical margins, or two or more involved lymph nodes to radiation therapy with either weekly cetuximab and cisplatin (30 mg/m^2) or weekly cetuximab and docetaxel (15 mg/m^2). Cetuximab was safely incorporated into both treatment regimens. The cetuximab/docetaxel arm was better tolerated and had improved disease-free and overall survival compared with cetuximab/cisplatin and historical controls. The regimen of cetuximab/docetaxel is currently undergoing further study as part of an adjuvant phase II/III RTOG trial for resected stage III or IV SCCHN with high-risk features (RTOG 1216). Cetuximab alone in combination with radiation therapy is currently being investigated in patients with intermediate risk, resected SCCHN (RTOG 0920); future results may provide an additional indication for the use of cetuximab.

Other EGFR Monoclonal Antibodies

Several other monoclonal antibodies directed against the EGFR have been developed and tested in patients with SCCHN, although none to the same extent as cetuximab, and the advantage of these EGFR monoclonal antibodies over cetuximab remains to be defined. Panitumumab (Vectibix, Amgen Inc., Thousand Oaks, CA) is a human IgG2 monoclonal antibody targeting EGFR domain III that was shown to be safe in combination with intensity-modulated radiation therapy (IMRT) and chemotherapy in a phase I trial of stage III and IV SCCHN,[38] but met with limited success in patients with R/M-SCCHN. The SPECTRUM trial was an open-label, phase III, multicenter, international trial that randomized 657 patients with R/M-SCCHN to up to six 3-week cycles of cisplatin (100 mg/m^2 on day 1) and 5-

fluorouracil (1,000 mg/m^2 on days 1 to 4) with or without panitumumab (9 mg/kg on day 1). Patients in the panitumumab arm were given the option of continuing panitumumab as maintenance therapy. The study failed to meet its primary endpoint of overall survival, but the addition of panitumumab did improve progression-free survival to 5.8 months (95% CI 5.6 to 6.6) in the panitumumab group from 4.6 months (4.1 to 5.4) in the control group (HR 0.780, 95% CI 0.659 to 0.922; p = 0.0036). Grade 3 or 4 toxicities were higher in the panitumumab arm, notably skin and eye toxicity, diarrhea, hypomagnesaemia, hypokalemia, and dehydration. Fourteen patients (4%) on the panitumumab arm died during treatment, five of which (2%) were attributed to the drug; eight patients (2%) died in the control arm. Planned subset analysis suggested a possible preferential benefit of panitumumab for patients with p16-negative SCCHN (see section on “Lack of Predictive Biomarkers for Benefit of EGFR Monoclonal Antibodies”). The role that panitumumab may play in the clinical management of patients with R/M-SCCHN remains to be further defined.

Zalutumumab (formerly HuMax-EGFr; Genmab, Princeton, NJ), a human IgG1 monoclonal antibody targeting the EGFR domain III, has shown single-agent activity in patients with R/M-SCCHN[39,40] and prolonged progression-free survival compared with best supportive care.[39] The largest trial of zalutumumab was published in 2011 by Machiels and colleagues and randomized 191 patients with R/M-SCCHN and progressive disease on platinum therapy in a 2:1 fashion to zalutumumab or best supportive care with the option to receive methotrexate (maximum dose 50 mg/m^2 weekly). In order to exploit the observation that the characteristic rash associated with EGFR inhibitors can be an indication of treatment response, the dose of zalutumumab was individually titrated (after standard loading doses of 8 mg/kg followed by two weekly doses of 4 mg/kg) to a maximum dose of 16 mg/kg every 2 weeks to try and achieve a grade 2 rash. Based on survival analysis of 82 patients with a grade 2 to 3 rash and 78 patients with a grade 0 to 1 rash, maximum rash grade was not predictive of overall survival (8.0 months for grade 2 to 3, 95% CI 6.7 to 9.8, vs. 6.8 months for grade 0 to 1, 95% CI 6.1 to 1.7; HR for death 0.72, 95% CI 0.51 to 1.02; p = 0.068). Single-agent activity of zalutumumab was 6.3% compared with 1.1% in the best supportive care/methotrexate arm. As with panitumumab, progression-free survival but not overall survival was improved by zalutumumab. Median

overall survival was 6.7 months (95% CI 5.8 to 7.0) in the zalutumumab group and 5.2 months (4.1 to 6.4) in the control group (hazard ratio [HR] for death, stratified by WHO performance status, was 0.77, 97.06% CI 0.57 to 1.05; $p = 0.0648$). Progression-free survival was longer in the zalutumumab group (9.9 weeks) than in the control group (8.4 weeks; HR for progression or death, stratified by WHO performance status, was 0.63, 95% CI 0.47 to 0.84; $p = 0.0012$). A second, smaller, open-label, phase II study investigated the efficacy and safety of zalutumumab in patients with platinum-refractory R/M-SCCHN.[40] Ninety patients were enrolled; notably 23% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 2. Objective response rate for zalutumumab was 5.7%, and disease control rate (objective responses + stable disease) was 39.8%. Median overall survival was 5.3 months (95% CI [4.1, 7.1]), and median progression-free survival was 2.1 months (95% CI [2.0, 2.6]). Performance status, as would be expected, impacted survival outcomes: patients with an ECOG performance status of 0 to 1 survived a median of 6.3 months compared with 2.5 months for those patients with a performance status of 2.[40] Side effects of zalutumumab in both studies were consistent with those reported for other EGFR monoclonal antibodies.[39,40] Zalutumumab appears to have single-agent activity comparable to cetuximab. Although it statistically prolonged progression-free survival compared with best supportive care/methotrexate, the magnitude of the benefit is small and the clinical relevance of this benefit is questionable. Perhaps the clinical utility for zalutumumab will lie in the treatment of patients with a poor performance status who are not candidates for more aggressive treatment regimens.

Nimotuzumab (formerly h-R3; Oncoscience AG, Germany, and YM Biosciences Inc., ON, Canada) is a humanized anti-EGFR IgG1 monoclonal antibody that is approved for treating SCCHN in multiple countries in Asia, Africa, and South America.[41] Most of the trials of nimotuzumab have used it along with radiation therapy or chemoradiation therapy for LA-SCCHN.[42–44] A phase I trial using nimotuzumab in combination with radiation therapy in patients with SCCHN unsuitable for standard chemoradiation therapy confirmed activity of nimotuzumab by demonstrating decreased phosphorylation of the EGFR and was tolerated in this patient population.[42] An open-label, phase II study in India demonstrated improvement in long-term survival in patients who received nimotuzumab in combination with

radiation therapy or chemoradiation therapy. The trial randomized 92 treatment-naive patients (1:1) with advanced SCCHN into chemoradiation (CRT +/− nimotuzumab) or radiation (RT +/− nimotuzumab) group by investigator's discretion. Overall response was 100% with CRT + nimotuzumab, 70% with CRT, 76% with RT + nimotuzumab, and 37% with RT alone. Five-year overall survival was 57% with CRT + nimotuzumab, 26% with CRT ($p = 0.03$), 39% with RT + nimotuzumab, and 26% with RT alone ($p > 0.05$). Studies from Cuba also suggested a survival benefit for nimotuzumab when given along with radiation or chemoradiation therapy[44,45] with associated improvement in disease-related symptoms and QOL.[44] Notably, nimotuzumab does not cause significant skin toxicity, making it an attractive option compared with other EGFR monoclonal antibodies.

EGFR Tyrosine Kinase Inhibitors

Specific EGFR Tyrosine Kinase Inhibitors: Gefitinib and Erlotinib

Gefitinib (Iressa; AstraZeneca, Wilmington, DE) and Erlotinib (Tarceva; Genentech, Inc., South San Francisco, CA) are highly specific, reversible EGFR TKIs that have been studied in patients with SCCHN as part of definitive treatment and in patients with R/M-SCCHN, but neither drug has become part of standard practice.

Gefitinib (Iressa; AstraZeneca, Wilmington, DE) is a highly selective oral EGFR TKI with a single-agent response rate of 7% to 11% in phase II trials of R/M-SCCHN[46]–[49]; escalating the dose of gefitinib to achieve a rash greater than or equal to grade 2 did not alter the response rate.[49] A single phase II trial of gefitinib for the treatment of platinum-refractory nasopharynx cancer showed no activity.[50] A single phase I trial showed promising results with the combination of gefitinib and celecoxib, but this combination was not pursued in subsequent clinical trials. Two phase III trials have investigated the activity of gefitinib in patients with R/M-SCCHN.[51,52] The first trial published in 2009 randomized 486 patients to gefitinib (250 mg/day), gefitinib (500 mg/day), or methotrexate (40 mg/m^2 IV weekly). There were no significant differences in response rate or overall survival across all arms, and the gefitinib arms had increased rates of tumor bleeding events compared

with methotrexate (8.9%, gefitinib 250 mg/day; 11.4%, gefitinib 500 mg/day; 1.9%, methotrexate).[51] Given promising preclinical and phase I data of the combination of docetaxel and EGFR TKIs,[53,54] a phase III trial through the ECOG was conducted investigating the efficacy of docetaxel and gefitinib in patients with previously treated R/M-SCCHN. A total of 270 patients were randomized to receive weekly docetaxel plus either placebo (arm A) or gefitinib 250 mg/day (arm B) until disease progression. Patients in the placebo arm were allowed to receive gefitinib at the time of disease progression. The study was closed early due to lack of benefit. Median overall survival was 6.0 months in arm A versus 7.3 months in arm B (HR, 0.93; 95% CI, 0.72 to 1.21; $p = 0.60$).[52]

Multiple phase I and II trials demonstrated the feasibility of adding gefitinib to definitive radiation therapy[55] or chemoradiation therapy[56–59] for patients with stage III and IV SCCHN without clear benefit and with potential increased toxicity.[57,60] Three phase II trials utilized gefitinib concurrent with definitive chemoradiation therapy for LA-SCCHN followed by maintenance gefitinib with mixed responses.[61–63] No benefit was seen when gefitinib was used in combination with hyperfractionated radiation, cisplatin, or 5-fluorouracil, followed by gefitinib maintenance,[61] or when gefitinib was combined with standard cisplatin and radiation followed by maintenance gefitinib.[62] A possible benefit, compared with historical controls, was seen when gefitinib was added to a regimen of split-course concurrent chemoradiation therapy with fluorouracil, hydroxyurea, and twice daily radiation therapy followed by maintenance gefitinib for 2 years.[63] Given the overall lack of benefit of gefitinib in patients with LA-SCCHN receiving radiation therapy or chemoradiation therapy and in patients R/M-SCCHN, treatment with this agent is not considered an acceptable standard practice.

Erlotinib has been studied in R/M-SCCHN as a single agent, in combination with cytotoxic chemotherapy, and in combination with other targeted agents. Although an early study of erlotinib as neoadjuvant therapy in an untreated patient population showed encouraging results with a single-agent response rate of 29%,[64] the activity of erlotinib in patients with R/M-SCCHN is modest and consistent with that seen with gefitinib. The best evidence for single-agent activity of erlotinib comes from a multicenter phase II study published in 2004 in the *Journal of Clinical Oncology* of 115 patients

with R/M-SCCHN treated with erlotinib that showed an overall response rate of 4.3% (95% CI, 1.4% to 9.9%) and disease stabilization in 38.3% of patients for a median duration of 16.1 weeks.[65] Erlotinib in combination with chemotherapy for patients with R/M-SCCHN did not appear to have any additional benefit over other regimens. The combination of erlotinib and docetaxel was not tolerated,[66] and a phase I/II trial reported a 21% response rate for the combination of erlotinib and cisplatin, consistent with established regimens in this patient population.[67] Erlotinib maintenance therapy after treatment with platinum and gemcitabine for recurrent nasopharynx cancer was not effective.[68] The combination of erlotinib and temsirolimus was poorly tolerated and led to early closure of the study. Erlotinib and bevacizumab were investigated in a phase I/II trial and showed a 14% response rate in the phase II portion, including four patients with a complete response. Median time of overall survival and progression-free survival were 7.1 months (95% CI 5.7 to 9.0) and 4.1 months (2.8 to 4.4), respectively.[69] Unfortunately, there were three patients with significant bleeding events, which likely limit the routine use of this combination.

Multiple phase I and II trials demonstrated the feasibility of erlotinib in combination with chemoradiation therapy for LA-SCCHN as definitive treatment[70]–[72] and in the adjuvant setting.[73] The largest study by Martens and colleagues randomized 204 patients with LA-SCCHN to standard radiation therapy with concurrent high-dose cisplatin with or without erlotinib 150 mg daily. Although erlotinib did not significantly increase the treatment toxicity, it failed to improve efficacy endpoints of complete response rate or progression-free survival.[70] Two studies used both erlotinib and bevacizumab in combination with chemoradiation therapy,[74,75] with one study reporting an increased risk of osteoradionecrosis.[74] Two phase I studies also showed the feasibility of using erlotinib in combination with reirradiation for recurrent SCCHN, one in combination with celecoxib.[76,77] Two phase III trials using erlotinib were attempted but closed early due to poor accrual—one in combination with first-line chemotherapy for R/M-SCCHN and a second as maintenance monotherapy for resected disease (NCT00448240 and NCT00412217). As with gefitinib, the overall modest activity of erlotinib did not lead to approval of its use in treating patients with cancer of the head and neck.

Dual and Pan-ErbB Tyrosine Kinase Inhibitors

Single-agent TKIs that target multiple ErbB family receptors are known as dual or pan-ErbB TKIs. Several of these agents—lapatinib, afatinib, and dacomitinib—are being studied in patients with SCCHN in both the locally advanced and metastatic settings. Lapatinib (Tykerb; GlaxoSmithKline, Research Triangle Park, NC) is a reversible TKI that targets both EGFR and HER2. A phase II study that gave 107 treatment-naive patients with SCCHN lapatinib or placebo prior to chemoradiation therapy reported a response rate of 17% with a decrease in tumor proliferation rate as measured by Ki-67 immunostaining.[78] When lapatinib was tested as monotherapy in patients with R/M-SCCHN, however, no significant antitumor activity was noted in either patients without prior EGFR exposure (arm A) or with prior EGFR exposure (arm B).[79] In an intent-to-treat analysis, no complete or partial responses were observed, and stable disease was the best response observed in 41% of arm A (median duration, 50 days, range, 34 to 159) and 17% of arm B subjects (median, 163 days, range, 135 to 195). Median progression-free survival was 52 days in both arms. Median overall survival was 288 (95% CI, 62 to 374) and 155 (95% CI, 75 to 242) days for arms A and B, respectively. Collectively, these studies suggest that any benefit for lapatinib in SCCHN may be as part of initial therapy. A phase I study established the dose of lapatinib with chemoradiation therapy for patients with SCCHN to be 1,500 mg/day.[80] A recently published placebo-controlled phase II trial of lapatinib given concurrent with chemoradiation and then as maintenance therapy showed a numerical improvement in the 6-month complete response rate—the primary endpoint of the study—from 36% with placebo to 53% with lapatinib ($p = 0.093$).[81] The secondary endpoints of progression-free and overall survival at 18 months were also improved from 41% to 55% (PFS) and 57% to 68% (OS) for placebo and lapatinib, respectively. Interestingly, p16-negative patients appeared to have a marked improvement in progression-free survival with lapatinib versus placebo (>20.4 months vs. 10.9 months).[81] The results of several phase II and III studies incorporating lapatinib into initial therapy for LA-SCCHN are pending, and will hopefully help to define the role of this agent in the future treatment strategies for patients with LA-SCCHN.

Afatinib (Giotrif; Boehringer Ingelheim, Ingelheim, Germany) and dacomitinib (PF-00299804; Pfizer Inc, New York, NY) are irreversible TKIs

that target EGFR, HER2, and HER4[82,83] and likely HER3 given the requirement for HER3 to heterodimerize with other ErbB family receptors. A randomized, crossover, phase II study compared single-agent afatinib to cetuximab. Patients treated with afatinib had increased adverse events leading to treatment discontinuations and dose reductions, but the agents were equivalent across all efficacy endpoints. In the 68 patients who crossed over to the other therapy upon disease progression, disease control rate was 33.3% for afatinib and 18.8% for cetuximab, suggesting a lack of cross-resistance in some patients with sequential treatment with different EGFR inhibitors.[84] Presently, a randomized, phase III trial (LUX Head & Neck 1) is investigating the efficacy of single-agent afatinib versus methotrexate in patients with platinum-resistant R/M-SCCHN.[85] Other phase II and III trials are under way to determine the potential benefit of afatinib as part of neoadjuvant, adjuvant, and maintenance therapy.

Dacomitinib has been studied in one open-label, multicenter, single-arm phase II trial in patients with R/M-SCCHN.[86] Sixty-nine patients were enrolled and received dacomitinib 45 mg orally daily. Partial response rate to dacomitinib was 12.7%, and 57.1% of patients had stable disease (14.3% lasting ≥24 weeks). The median progression-free survival was 12.1 weeks and the median overall survival was 34.6 weeks. The most common grade 3 or higher treatment-related adverse events were diarrhea (15.9%), acneiform dermatitis (8.7%), and fatigue (8.7%). Approximately 40% of patients required either a dose reduction or a treatment interruption secondary to drug toxicity.[86] Preclinical data support the use of dacomitinib along with radiation therapy for the treatment of SCCHN[87] and in cetuximab-resistant SCCHN,[88] but no clinical trial data are yet available.

Mechanisms of Resistance to EGFR Inhibition

Collectively, all of the evidence for EGFR inhibition, despite the overexpression of EGFR in most SCCHN, shows a relatively modest benefit in terms of treatment response and survival. The presence of primary or acquired resistance to EGFR-targeted therapy is likely a factor in mitigating the success of these agents. Recent preclinical and clinical investigations have demonstrated several possible mechanisms leading to resistance to EGFR inhibition including activation of other ErbB family receptors (e.g., HER2 and HER3) and activation of other signaling pathways such as

vascular endothelial growth factor (VEGF), the hepatocyte growth factor (HGF)/ c-MET pathway, and the Notch pathway.[89–96] Preclinical data of the role of the insulin-like growth factor receptor (IGFR) pathway have been mixed.[97–99] Activation of downstream signaling pathways has also been implicated in resistance to EGFR inhibition including the PI3K/AKT pathway, RAS/MAPK/ERK pathway, mammalian target of rapamycin (mTOR) pathway, and the signal transducer and activator or transcription 3 (STAT3) pathway.[100–102] Other mechanisms of resistance have been described as well including the potential benefit of the combination of EGFR and cyclooxygenase-2 (COX-2) inhibition, epigenetic events such as hypermethylation of death-associated protein kinase (DAPK), and nuclear EGFR expression.[103–105]

Several novel agents are now being studied in phase II and III trials to try and overcome EGFR resistance in the clinical setting. There are many new drugs that have been designed to target more than one receptor in an effort to increase clinical efficacy. Several of these agents including lapatinib, afatinib, and dacomitinib have already been discussed (see section “Dual and Pan-ErbB Tyrosine Kinase Inhibitors”). Vandetanib (Caprelsa; AstraZeneca Pharmaceuticals LP, Wilmington, DE) is an oral TKI that targets both EGFR and VEGF receptor 2. Vandetanib in combination with docetaxel in platinum-refractory patients with SCCHN was not found to be effective,[106] but it is currently being studied in combination with chemoradiation therapy for patients with LA-SCCHN (NCT00720083). The monoclonal antibody MEHD7945A (Genentech, Inc., South San Francisco, CA) targets both EGFR and HER3 and showed promising results in a phase I trial where 20% of patients with R/M-SCCHN achieved a partial response (abstract only). It is currently being compared to cetuximab in a randomized phase II trial in patients with R/M-SCCHN (NCT01577173).

Novel therapeutic combinations using an EGFR inhibitor in combination with other targeted therapies have been investigated or are under active investigation. Dual inhibition of the EGFR and vascular endothelial growth factor receptor (VEGFR) has shown responses in patients with R/M-SCCHN.[69,94] The combination has also been used along with CRT for patients with LA-SCCHN,[74] albeit with potential increased toxicity.[74,75] Multiple ongoing phase II trials are investigating the use of EGFR and VEGF inhibition in patients with R/M- and LA-SCCHN (NCT00392665,

NCT00968435, NCT00703976). Dual inhibition of the EGFR and mTOR pathways is ongoing in patients with R/M-SCCHN (NCT01256385, NCT0128334, NCT00942734), despite initial phase I/II data showing poor patient tolerability and a short progression-free survival.[107] The TKI dasatinib (Sprycel; Bristol-Myers Squibb, Princeton, NJ), despite having multiple targets including BCR-ABL, stem cell factor receptor (c-KIT), platelet-derived growth factor receptor (PDGFR), and Src family kinases, showed no responses when used as monotherapy for patients with R/M-SCCHN[108] but is being investigated concurrent with and after failure of cetuximab-based radiation therapy (NCT00882583, NCT01488318). Sorafenib (Nexavar; Bayer, Leverkusen, Germany) and sunitinib (Sutent; Pfizer Inc., New York, NY) both target multiple protein kinases but have shown poor activity and significant side effects when studied in patients with R/M-SCCHN[109–111]; tivantinib (formerly ARQ 197) is a c-MET inhibitor currently under active investigation in combination with EGFR inhibitors (see “c-MET” section below for more details). Phase I data for the use of the COX-2 inhibitor celecoxib (Celebrex; Pfizer, Inc., New York, NY) along with an EGFR inhibitor demonstrated a 22% response rate in patients with R/M-SCCHN and showed promising activity along with reirradiation for recurrent SCCHN,[77,112] but there are no current ongoing trials of this combination.

c-MET

The HGF/c-MET pathway has been shown to be involved in the pathogenesis and progression of SCCHN.[113–124] The HGF is a peptide growth factor that is secreted by mesenchymal cells and acts primarily on epithelial cells where it binds to the c-MET receptor and, through activation of multiple downstream pathways, regulates cell growth, motility, and invasion. Serum HGF and HGF concentration in tumor tissue has been shown to be significantly elevated in patients with SCCHN and is associated with tumor progression and recurrence.[113,115] Silencing Met receptor tyrosine kinase signaling through Met knockdown in established SCCHN cell lines impaired activation of downstream MAPK signaling, reduced tumor growth by increased cell apoptosis, decreased regional lymph node metastases, and increased survival of nude mice with orthotopic xenografts.[125] Increased expression of c-MET has been associated with poor response to radiation

therapy in patients with SCCHN.[126] c-MET expression in some studies has been associated with lymph node metastasis, advanced tumor stage, risk of recurrence, and decreased survival.[119,124,127] More recent studies using archival tissue of patients treated for SCCHN identified increase c-MET expression by immunohistochemistry (57% to 58%) but found no significant correlation of c-MET expression on treatment response or survival.[128,129]

Recent data suggest that the HGF/c-MET pathway may play a more critical role in HPV-negative head and neck cancers.[130] The role of HGF and c-MET expression and *c-MET* gene copy number in HPV-negative and HPV-positive tonsil cancers was recently investigated. HGF overexpression was found to be an independent prognostic factor for decreased survival in HPV-negative but not HPV-positive tumors. Neither c-MET overexpression nor *c-MET* copy number was associated with survival outcomes in either cohort.[130] Baschnagel and colleagues examined archival tissue for 107 patients with SCCHN treated with chemoradiation and correlated c-MET expression with p16 status and clinical endpoints. High c-MET expression predicted for worse disease-free survival in p16-negative but not p16-positive patients.[131]

Inhibitors of c-MET in clinical development include the small molecule tivantinib and the monoclonal antibody ficlatuzumab. Two phase I studies of single-agent tivantinib included patients with head and neck cancer (total 2 nasopharynx, 3 SCCHN) without any reported partial responses.[132,133] It was not specified in the manuscripts whether any of them had stable disease. A phase I study of the c-MET inhibitor tivantinib (formerly ARQ 197) in combination with gemcitabine in advanced solid tumors reported a 20% partial response rate and 46% rate of stable disease; one of the patients with a partial response had squamous cell of the oral tongue carcinoma.[134] A phase I study of tivantinib in combination with erlotinib included 3 head and neck patients, one of whom had a partial response and two who had disease control for 7 and 8 months, respectively.[135] Ongoing studies of c-MET inhibitors include a randomized phase II trial of cetuximab with or without tivantinib in patients with R/M-SCCHN (NCT01696955), a trial of INC280 plus cetuximab in c-MET-positive SCCHN or colorectal cancer (NCT00205398), a trial of cetuximab with or without E7050 in platinum-resistant SCCHN, and a trial of definitive therapy for LA-SCCHN using IMRT, cisplatin, and ficlatuzumab (NCT02277184).

The future of c-MET inhibition as a therapeutic option for patients with SCCHN appears promising. It remains to be determined exactly which subset of patients with SCCHN will benefit from inhibition of the c-MET pathway; perhaps more studies in the HPV-negative oropharynx cancer population are warranted in the future. Lim and colleagues demonstrated that activation of c-MET is critical for the proliferation and maintenance of cancer stem cell traits in SCCHN and suggest that c-MET inhibition should be investigated as a therapeutic strategy to target SCCHN stem cells. As with all targeted therapies in the treatment of cancer, identifying the subset of patients with a high likelihood of benefit is key.

Fibroblast Growth Factor Receptor

The fibroblast growth factor receptor (FGFR) is a family of receptor tyrosine kinases that are regulators of a variety of cellular processes that include proliferation, migration, survival, and angiogenesis.[136] The ligand for the FGFR is fibroblast growth factor (FGF), a soluble growth factor that binds to the FGFR and also plays a role in epithelial–mesenchymal transition (EMT), a process through which cells acquire the ability to invade and migrate.[137] Abnormalities in the FGR or the FGFR have been shown to be key drivers of tumorigenesis in breast cancer.[138,139] A marker of EMT is the loss of the adhesion molecule E-cadherin. Several preclinical studies provide a strong rationale for targeting the FGFR in SCCHN.[137,140–145] Nguyen et al. [137] recently investigated the expression of FGFR1 in SCCHN and the role of the FGFR1 inhibitor PD173074 in EMT and tumorigenesis. Preclinical data from six head and neck cancer cell lines identified three of the cell lines that were found to be EMT induced, characterized by loss of E-cadherin and expression of the EMT genes Snail1, Snail2, ZEB1, and ZEB2. FGFR1 was found to be strongly expressed in the EMT-induced but not the non–EMT-induced cell lines. In the EMT-induced cell lines, PD173074 inhibited the autophosphorylation of FGFR1 in a dose-dependent manner and suppressed SCCHN cell growth, invasion, and migration. Cells treated with PD173074 showed decreased activation of ERK1/2, suggesting downstream inhibition of the MAPK pathway. In 100 tumor samples from patients with SCCHN, 54% highly expressed the FGFR1, and FGFR1 expression was found to correlate with increased nuclear polymorphism, increased invasion, and high-grade histology.[137] Large-scale sequencing projects have identified FGFR as a

potentially valuable target for cancer therapies for SCCHN.[140,141] Seiwert and colleagues recently published genomic analyses of HPV-positive and HPV-negative SCCHN using pretreatment tumor samples and matched normal DNA from patients with LA-SCCHN and found that potentially targetable somatic mutations in the genes *FGFR2* and *FGFR3* were identified in 17.6% of HPV-positive tumors. In HPV-negative patients, one tumor sample showed amplification of *FGFR1*.[140] Preclinical data in an SCCHN xenograft model identified up-regulation of the FGFR as a contributor to bevacizumab resistance,[142] and the combinations of FGFR inhibition and inhibition of ERBB2 and MET showed decreased growth of SCCHN cell lines in vitro.[143] Multiple phase I studies in solid tumors are investigating the use of FGFR inhibitors. A phase II trial of ponatinib (Iclusig), an oral FGFR tyrosine kinase inhibitor, in patients with lung and SCCHN with FGFR kinase alterations was opened but is presently suspended (NCT01761747). Future trials of FGFR inhibitors alone or in combination with other pathway inhibitors such as EGFR or c-MET seem warranted.

The Phosphoinositide-3 Kinase Pathway (PI3K/AKT/mTOR)

The PI3K/AKT/mTOR signaling pathway is part of many normal physiologic processes and associated with a number of oncogenic processes. In fact, collectively, members of the pathway are among the most frequently altered pathways in cancer, including SCCHN.[146] The PI3K family of enzymes can be divided into three classes (I to III).[147] Class I PI3Ks are heterodimers comprising regulatory and catalytic subunits. The latter include isoforms, p110α (*PIK3CA* gene), p110β, p110δ, and p110γ. Class I PI3Ks are the most commonly altered in cancer and have been investigated as therapeutic targets.

Once activated, PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2), generating phosphatidylinositol (3,4,5)-trisphosphate (PIP_3).[147] PIP_3 initiates AKT activation by its translocation to the plasma membrane, which further phosphorylates multiple proteins including those responsible for protein synthesis and cell growth through the mTOR complex (mTORC) 1. A second mTOR complex, mTORC2, also directly phosphorylates AKT on serine 473.[147]

Whole-exome sequencing data from locally advanced SCCHN revealed that the PI3K pathway is mutated in approximately one-third of tumors.[148] Altered genes include *PIK3CA*, *PIK3CD*, *PTEN*, *PDK1*, *AKT*, and *mTOR*.[148–154] In addition, *PIK3CA* amplifications and *PTEN* inactivation are also common in SCCHN. Moreover, this pathway appears to be commonly dysregulated in HPV-related SCCHN[155] with one study demonstrating *PIK3CA* mutations in 31%, *PIK3CA* amplifications in 20%, and PTEN loss in 33% of cases.[156] The Cancer Genome Analysis recently completed work on SCCHN revealing *PIK3CA* mutations in 21% of all samples with 40% to 50% of HPV-related tumors harboring an alteration in *PIK3CA*.[157]

PI3K Inhibitors

Agents that target all four class I PI3K isoforms, including buparlisib (BKM120; Novartis Pharmaceuticals Corporation, East Hanover, NJ) and PX-866 (Oncothyreon, Seattle, WA), have been investigated in SCCHN. Buparlisib has demonstrated in vitro and in vivo efficacy in SCCHN models and is currently in clinical trials.[158] PX-866 is another agent that has demonstrated antitumor efficacy in SCCHN models with *PIK3CA* alterations.[159] Two phase II trials have been completed adding PX-866 to docetaxel or cetuximab, respectively.[160,161] In neither study did the combination arm with PX-866 provide an improvement in response rate, progression-free survival, or overall survival compared to docetaxel or cetuximab alone. These studies, however, did not preselect subjects based on genomic or pathway activation.

BYL719 (Novartis Pharmaceuticals Corporation, East Hanover, NJ) is an oral inhibitor that selectively targets the α isoform of class I PI3K.[162] In a phase I study of BY719 in patients with *PIK3CA*-mutated tumors, SCCHN patients were among those with an observed partial response and demonstrated the greatest reductions in tumor volume.[163] Based on preclinical data,[164] a phase I/II study of BYL719 and cetuximab in patients with recurrent or metastatic SCCHN is currently ongoing (NCT01602315).

mTOR Inhibitors

Everolimus (Afinitor, Novartis Pharmaceuticals Corporation, East Hanover, NJ) is an mTORC1 inhibitor and is being tested as part of a phase I/II study

investigating induction chemotherapy with weekly everolimus, carboplatin, and paclitaxel in locally advanced SCCHN (NCT01333085). Preliminary data suggest that treatment is well tolerated with an overall response rate of 79%.[165] Temsirolimus (TORISEL, Wyeth Pharmaceuticals Inc., Madison, NJ), another mTORC1 inhibitor, was added to carboplatin and paclitaxel in a phase I study in patients with recurrent/metastatic SCCHN and achieved an objective partial response rate of 22%.[166] In a phase II study in patients with recurrent or metastatic, platinum-refractory SCCHN, the combination of temsirolimus plus erlotinib was poorly tolerated and prematurely aborted providing some caution in employing EGFR and mTOR targeting.[107]

Cyclins D1 Function and Inhibitors

The mammalian cell cycle is regulated by cyclin-dependent protein kinases (CDKs). CDKs are often hyperactivated in cancer, thus representing potential small-molecule targets in several malignancies. Retinoblastoma (Rb) pocket proteins p107 and p130 prevent the cell from replicating damaged DNA by controlling the restriction point that would allow the progression along the cell cycle through G1 into S. Rb binds and inhibits transcription factors of the E2F family, which are composed of dimers of an E2F protein and a dimerization partner (DP) protein. The transcription activating complexes of E2F–DP can push a cell into S phase. When Rb is bound to E2F, the complex acts as a growth suppressor and prevents progression through the cell cycle keeping the cell stalled in the G1 phase. However, in response to a mitogenic signal, the cyclin D1–CDK4 and cyclin D1–CDK6 complexes are activated. These induce phosphorylation of the Rb protein, resulting in release (and therefore activation) of E2Fs and thereby promoting transcription of genes that trigger S phase entry. On the other hand, the CDKN2A gene encodes for the protein p16, an inhibitor for the cyclin D1–CDK4 complex that mediates senescence and differentiation. Consequently, the interplay between the cyclins, CDKs, and their inhibitors determines whether the restriction point can be passed.[167]

Increased expression and gene amplification of cyclin D1 have been observed in 68% and 58% of SCCHN of the tongue, both findings associated with a worse disease-free and overall survival.[168,169] Similarly, loss of p16INK4A has been reported in 55% of anterior tongue tumors and has also been associated with worse outcome.[168] Preclinical studies have reported that

deregulated cyclin D1 overexpression may be associated with resistance of HNSCC to the EGFR kinase inhibitor gefitinib.[169] Therefore, inhibitors of cyclin D1 and other regulatory CDKs are attractive agents to developed in SCCHN.

Seliciclib (CYC202; R-roscovitine) is an orally available inhibitor of CDK2/E, CDK2/A, CDK7, and CDK9 that has been shown to enhance apoptosis in head and neck cancer cells in preclinical studies.[170] It was the first CDK inhibitor to enter the clinic, and two phase I studies were developed using continuous and intermittent doses of seliciclib in patients with solid tumors. Both trials treated a total of 77 patients, but there was only one objective response seen in one patient with hepatocellular carcinoma. No patients with SCCHN were treated in either trial.[171,172] Another small trial evaluated seliciclib in 14 patients with nasopharyngeal carcinoma, reporting grade 3 liver toxicity in one patient and grade 2 vomiting on another at doses of 800 mg twice daily, but no significant toxicities were experienced in 13 patients treated at 400 mg twice daily. Seven of 14 evaluable patients had clinical evidence of tumor reduction. Some of these responses were associated with increased tumor apoptosis, necrosis, and decreases in plasma EBV DNA posttreatment.[173] Another orally bioavailable CDK inhibitor, LEE011, that targets cyclin CDK4/6 is currently being tested in patients with solid tumors and amplifications or mutations of CDK4/6.

Apoptosis and Poly(ADP-Ribose) Polymerases (PARPs) Inhibitors

In the presence of DNA damage, a normal cell will prompt cell cycle arrest while the potential for repair is assessed. If the damage exceeds repair capacity, the cell will then undergo programmed cell death (apoptosis). Whereas an immune-mediated pathway can trigger antigen-induced cell death, an intrinsic or mitochondrial pathway can also activate apoptosis in response to unrepaired DNA damage. Poly(ADP-ribose) polymerases (PARPs) are a family of enzymes involved in DNA repair for cell survival and apoptosis. PARP1 is the most studied of these enzymes and accounts for at least 85% of maximally activated cellular PARP activity. Their main role is to detect and signal single-strand DNA breaks (SSB) and consequently recruit proteins responsible of the enzymatic machinery of DNA repair. The

typical activation pathway for PARP1 is triggered by DNA breaks caused by ROS/RNS species, UVB, or ionizing radiation. Once PARP detects an SSB, it binds to DNA and begins the synthesis of a poly(ADP-ribose) chain (PAR) as a signal for DNA repair enzymes such as DNA ligase III and DNA polymerase beta.[174] Because survival of cancer cells depends on their ability to continually repair their own DNA, blocking the antiapoptotic regulators of the intrinsic pathway with novel PARP inhibitors represent a potentially attractive new therapeutic option in a range of malignancies, including SCCHN.

Inhibition of PARP blocks the repair of spontaneous SSB, leading to the formation of double-strand breaks through mechanisms such as stalled replication forks. These double-strand breaks become lethal in cells that are deficient in double-strand break repair (such as those with mutations in BRCA1 or BRCA2).[175] PARP inhibitors can also trap the PARP1 and PARP2 enzymes at damaged DNA. With unrepaired SSB, the trapped PARP–DNA complexes are highly cytotoxic and can induced block of DNA replication.[176] Thus, several PARP inhibitors are currently being evaluated in clinical trials as single agents or in combination with other cytotoxic agents or radiation therapy. PARP1 protein has been found to be highly expressed in nasopharyngeal carcinoma cell lines and the level of expression strongly correlates with nasopharyngeal carcinoma disease stage. In preclinical studies, the PARP inhibitor olaparib (AZD2281) can increase DNA damage, cell cycle arrest, and apoptosis in nasopharyngeal carcinoma cells challenged with ionizing radiation or temozolomide, as well as enhance the tumor inhibitory effects of ionizing radiation in animal xenograft models.[175] Double-strand breaks (DSBs) are repaired mainly by homologous recombination during replication. Some SCCHN have been reported to have a deficiency in homologous recombination, a characteristic that can act phenotypically as a BRCA germline mutation. The presence of this abnormality in some SCCHN cell lines has been correlated to susceptibility to PARP inhibitors, especially with rucaparib.[177] Moreover, when used in combination with radiation therapy, PARP inhibitors have synergistic activity enhancing apoptosis in vitro and in vivo, as compared with radiation alone.[178,179]

Veliparib (ABT-888, NSC 737664) is an orally available PARP inhibitor that has been combined with carboplatin and paclitaxel in a phase I trial. The

combination was found to be well tolerated and with a safety profile similar to the chemotherapy doublet without veliparib. Of the seven patients with SCCHN that were included, one had a partial response.[180] Studies using olaparib concurrently with radiation for patients with locally advanced SCCHN are in development.

Angiogenesis

Angiogenesis plays an essential role in tumor growth and metastasis; therefore, controlling tumor-associated angiogenesis is now a key tactic in limiting cancer progression. VEGF is a subfamily of structurally related growth factors that can increase vascular permeability and promote proliferation and survival of endothelial cells. All members of the VEGF family can stimulate cellular responses by binding to the VEGFRs on the cell surface, causing dimerization and subsequent activation through transphosphorylation, but VEGF-A is the most important mediator of angiogenesis and contributor to pathogenesis in many cancers.[181] VEGF-A promotes angiogenesis mainly via VEGF receptor 2 (VEGFR2). The binding of VEGF to VEGFR2 leads to dimerization of the receptor, followed by intracellular activation of a cascade of different signaling pathways such as Raf/MAPK and phosphatidylinositol 3′ kinase (PI3K)-Akt pathways.[182]. In SCCHN, VEGF protein overexpression has been associated with a worse OS in SCCHN patients.[183,184] In a preclinical study, the inhibitors of VEGFR2 and PDGFR sorafenib and sunitinib lead to a statistically significant down-regulation of PDGFR α/β in HPV-positive SCCHN cell lines, but not in HPV-negative tumor cells. HPV-positive HNSCC, consequently, might exhibit a higher sensitivity to antiangiogenesis drugs compared to HPV-negative HNSCC.[185]

Several antiangiogenesis drugs are currently approved and in clinical use for the treatment of malignancies, but none so far in SCCHN. Bevacizumab, a monoclonal antibody directed against VEGF, is approved in the United States and Europe for use in metastatic lung cancer, colorectal cancer, and glioblastoma. Interestingly, in non–small cell lung cancer (NSCLC), bevacizumab is only approved for its use in nonsquamous histology because of the bleeding risk associated with squamous cell carcinomas of the lung. Bevacizumab has been studied in SCCHN in the metastatic setting added to chemotherapy with pemetrexed. A phase II trial enrolled 40 patients with

recurrent and metastatic SCCHN and using bevacizumab added to chemotherapy with pemetrexed. The median OS was 11.3 months and the ORR was 30%.[186] There were, however, bleeding events in 15% of the patients, but not all of them were considered treatment related. VEGF signaling is up-regulated by EGFR expression, and up-regulation of VEGF has been associated with resistance to cetuximab.[187,188] Thus, cotargeting of EGFR and VEGF has been attempted in patients with SCCHN. Bevacizumab was combined with cetuximab in a phase II trial enrolling 46 patient, reporting a disease control rate of 73% and ORR of 16%.[186] Median PFS and OS in the trial were 2.8 and 7.5 months, respectively, and <10% of the patients had grade 3 to 4 adverse events. Similar results were seen in a phase I/II trial that combined erlotinib with bevacizumab, where an RR of 15% and OS of 7.1 months were seen in the 48 patients enrolled.[69]

An alternate approach to block angiogenesis is using low molecular weight inhibitors of the tyrosine kinase domain of VEGFR2. Several of these inhibitors are commercially available and approved for diseases as renal cell carcinoma, hepatocellular carcinoma, and refractory thyroid cancer. Vandetanib (ZD6474), a multikinase inhibitor of EGFR, VEGFR2, and RET, has demonstrated antitumor activity on nude mice bearing an established xenograft of SCCHN cells by inducing apoptosis and decreasing angiogenic activity.[189] Vandetanib was also combined with docetaxel in a phase II trial that treated patients with metastatic/refractory SCCHN. The trial randomized 29 patients that failed platinum-based therapy to docetaxel every 3 weeks with or without vandetanib orally daily. There was no difference between PFS or OS, although a small statistically significant difference in response rate was noted.[106] Another phase I/II study added vandetanib with radiation therapy with or without cisplatin in patients with locally advanced disease and enrolled 33 patients. All the 29 patients that were evaluable for efficacy achieved a complete response and of the 17 patients that completed a 2-year follow-up at the time of the presentation, 6 recurred, and 11 remained free of disease.[190] Four of the 18 patients that received vandetanib discontinued therapy due to adverse events.

Sorafenib is another small molecular inhibitor of VEGFR, PDGFR, and Raf kinases. It was evaluated in the recurrent/metastatic setting in a phase II trial that enrolled 41 patients, reporting a median PFS of 4 months and OS of 9 months, but with only 2% of RR. The most common side effects included

fatigue, anorexia, stomatitis, hand–foot syndrome, and hypertension.[110] More encouraging results were seen on another phase II trial that combined sorafenib with paclitaxel and carboplatin, achieving an RR of 55%, disease control in 84%, and median OS of 22 months.[191] Grade 3 adverse effects included hand–foot syndrome, neutropenia, elevated lipase, amylase, and anemia.

Sunitinib is also a multikinase inhibitor with activity against VEGFR2, PDGFR, RET, and c-KIT. Two A phase II trial evaluated sunitinib monotherapy in patients with recurrence metastatic SCCHN. The first one treated 38 patients, reporting a disappointing OS of 3.4 months and partial response in one patient and grade 3 or more bleeding episodes in 16% of the patients treated.[192] The second study accrued 22 patients, achieving a patient response in one.[111]

Immunotherapy for SCCHN

Another manner of targeting SCCHN has aimed at targeting the immune system. Therapies that modulate the immune system in SCCHN may be particularly active as these patients are deemed relatively immunosuppressed. Patients with SCCHN, compared to healthy controls, demonstrate lower absolute numbers of CD3+, CD4+, and CD8+ T cells,[193] dysfunctional antigen-processing machinery,[194,195] and impaired natural killer cell activity.[4] As seen with other malignancies, patients whose cancer cells elicit an immune response appear to have a better prognosis; for example, the presence of tumor-infiltrating lymphocytes (TIL) has been identified as a good prognostic factor for SCCHN patients.[196,197] Regulatory T cells (T-regs) modulate the immune system and maintain tolerance to self-antigens by down-regulating the induction and proliferation of effector B and T cells.[198] An increase in the concentration of T-regs found in the periphery of patients with SCCHN appears to correlate with an improved prognosis.[199] Furthermore, chronic HPV infection plays a strong role in a subset of SCCHN patients, and it is well known that the same mechanisms that enable a chronic infection also promote malignant transformation. After an infection with HPV, the virus is usually cleared in the majority of individuals through T cell–mediated immunity. In a subset of patients, the infection persists, leading to chronic inflammation, inhibited cell growth, and immune

tolerance, which subsequently can lead to cellular malignant transformation.[200] The virus down-regulates the immune system through a variety of mechanisms. The viral proteins E5 and E7 down-regulate the expression and cell surface concentration of class I HLA.[201] Similarly, E6 and E7 reduce the effects of alpha and beta interferon (IFN).[202] Tobacco-related malignancies share a similar chronic inflammatory cellular milieu, which can contribute to and accelerate the malignant transformation.[203]

In order for a cancer to continue its growth, it has to succeed at modulating and suppressing a natural immune response. All cancer cells have genetic and epigenetic alterations that can present antigens that the immune system can exploit to attack while distinguishing malignant cells from benign ones. The mechanisms cancers employ to evade and avoid destruction by the immune response are extremely complex and involve multiple pathways including mechanisms of evasion, direct suppression, and indirect suppression. Evasion of the immune response can be achieved by a number of mechanisms, which include decreasing the expression of surface MHC class I molecules[204] or impairing antigen-processing machinery.[194] Direct immune suppression occurs through the expression of receptors normally found in immune cells that induce an antiapoptotic pathway or an inhibitory signal such as the Toll-like receptor 4 (TLR-4),[205] galectin-1,[206] FasL,[207] TRAIL,[208] and PD-L1.[209,210] Finally, indirect suppression and modulation of the immune response can be mediated through recruiting and directing a cellular network of cells such as tumor-associated macrophages, myeloid-derived suppressor cells, immature dendritic cells (DCs), regulatory T cells, and natural killer cells.[204]

The goals of immunotherapy are to reverse the mechanisms of immune resistance and augment the antitumor immune response as a therapeutic strategy. Immunotherapies can be divided in cytokine, antibody, and cell-based therapies. Cytokine therapies regulate and coordinate the response of the immune system and generally augment the response of an ongoing active immune system. Antibodies use antigens expressed by tumor cells to induce antibody-dependent cell–mediated cytotoxicity (ADCC), interfere with cell signaling by modifying the interaction of cell membrane receptors and its ligands, deliver a dose of chemotherapy or radiation to a specific target, or finally activate the complement system. In cell-based therapies, autologous immune cells are harvested from patients, activated in vitro, expanded, and

subsequently returned to the patient to elicit an immune response.

Although targeting the immune system with vaccines and other immune-stimulating agents has been a strategy employed for years in many tumor types, this strategy has not been met with much success in SCCHN, and some therapies also had considerable toxicity. However, recent breakthroughs with the immune checkpoint inhibitors have generated renewed enthusiasm in immunotherapy due to observed dramatic sustained tumor regressions, reasonable tolerability, and improvements in survival in solid tumors that had not been considered amenable to immune targeting, such as NSCLC.[211,212] Preliminarily, responses to the immune checkpoint inhibitors appear to be more prominent in those NSCLC patients with squamous cell histology[213] that share biologic similarities to SCCHN. The inflammatory milieu observed in SCCHN tumor specimens, the relative immunosuppression in SCCHN patients, and the limited effective systemic therapies available for recurrent or metastatic SCCHN support the exploration of, and renewed interest in, therapies targeting the immune system in SCCHN. An exhaustive list of immune therapies that have been attempted or examined will not be discussed—however, some of the more promising immunotherapies and immunotherapy trials will be presented.

Cytokines

Cytokines are a large family of proteins that are essential for cell signaling. The term cytokine is a general term used to describe chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors. Cytokines modulate inflammation and contribute to mediation of an immune response. Cytokines administered systemically have been used to elicit an immune response in malignancies such as melanoma and renal cell carcinoma. Despite antitumor responses and activity, they are associated with significant toxicities. In SCCHN patients, a number of cytokines have been explored and some of the notable cytokines of interest are subsequently presented; however, adoption of cytokine therapy in this patient population has been largely limited due to tolerability.

Systemic IL-2 administration coupled with IFN-alpha led to two partial responses in 11 heavily pretreated SCCHN patients; however, adverse events were substantial with grade 3 hypotension and fatigue being the most common reasons for discontinuing study therapy.[214] Local administration of

IL-2 appeared to be better tolerated; in a phase III trial, 220 patients underwent direct local administration of low-dose (5,000 U/day) perilymphatic recombinant IL-2 administered pre- and postoperatively in resectable SCCHN (T2 to T4, N0 to N3, M0); patients in the experimental arm had an improvement in both PFS and OS. Moreover, after a median follow-up of 64 months, the median OS for the experimental arm was not reached, in contrast to a median OS of 75 months in the standard of care arm ($p = 0.03$).[215] However, despite its low toxicity and improvements in survival demonstrating a role for immunotherapy in SCCHN, no tumor responses were observed, limited immunologic correlates were performed, and immunologic endpoints were not assessed, which hampered the adoption of IL-2 in this setting.

To optimize the delivery of IL-2, other formulations have been explored such as ALT-801. ALT-801 is a fusion protein that contains IL-2 coupled with a single chain T-cell receptor domain that targets tumors that overexpress the p53 gene. This therapy in a dose-escalating phase I study of 26 patients with a variety of solid tumors demonstrated lesser toxicities than those experienced in high-dose IL-2, with demonstrated biologic and immunologic correlative effects such as interferon-γ induction and encouraging clinical activity with stability in 10 patients lasting over 11 weeks. Notably, administration of two doses of ALT-801 at 0.04 mg/kg to a heavily pretreated progressing SCCHN patient led to disease stability for >8.5 months with no other anticancer treatment.[216]

Other active cytokines such as IL-12 and IL-15 were explored for their immunostimulatory effects with hopes of less toxicity. Il-12 injected into the primary tumor of 30 SCCHN patients in a phase II study showed immunologic correlative effects with a redistribution of NK cells, lymphocytes, and monocytes from the peripheral blood to lymph nodes and increased lymph node IFN-gamma expression levels. However, significant toxicity was experienced and no clinical responses were seen.[217] As preclinical in-vitro studies of IL-12 appeared to enhance the antitumor activity and ADCC effects of cetuximab and in vivo xenograft models demonstrated synergistic tumor regressions,[218] this combination is being currently investigated in a phase I/II study in SCCHN patients (NCT01468896). IL-15 is a cell growth factor that induces the activation and proliferation of CD8+ T cells as well as NK cells. It maintains long-term

memory T cells with relatively less effect on T regulatory cells and inhibits activation-induced cell death.[219] A phase I study is currently exploring the subcutaneous administration of IL-15 in patients with a number of solid malignancies, including SCCHN (NCT01727076).

Other cytokines such as interferon-alpha demonstrated promise but were limited by feasibility. Preliminary results of interferon-alpha coupled with isotretinoin and vitamin E administered in 45 SCCHN patients in a phase II trial demonstrated a 5-year progression-free survival rate of 80% and a 5-year overall survival rate of 81.3%.[220] Unfortunately, an ECOG-led phase III trial of this regimen was terminated due to poor accrual. IRX-2 is a product that contains a physiologic combination of cytokines that includes IL-2, IL-1-beta, IFN-gamma, and TNF-alpha. It is administered subcutaneously in the neck area just above and adjacent to the lymph nodes draining the head and neck. It demonstrated promising activity in a neoadjuvant phase II study of 42 SCCHN patients with 3 complete responses and 10 partial responses. A phase III study is under way in patients undergoing surgery for oral cavity cancers.[221]

Another class of agents that can potentially have a therapeutic effect in SCCHN are the Toll-like receptor (TLR) agonists. TLRs are also important mediators in the immune response that can have an immunostimulatory effect and antitumor activity. TLR agonists induce a potent innate and adaptive immune response and can enhance the ADCC activity of therapeutic monoclonal antibodies.[222,223] Preclinically, potent immunologic anticancer effects were observed with the TLR agonists in SCCHN models.[224–226] VTX-2337 is a small molecule TLR8 agonist that activates myeloid dendritic cells, monocytes, and natural killer (NK) cells. A phase Ib study with escalating doses of VTX-2337 and a fixed dose of cetuximab in 12 patients with previously treated SCCHN demonstrated a response rate of 16.7% and a disease control rate of 50%.[227] This encouraging study formed the basis for a subsequent randomized phase II study comparing 5FU, a platinum agent, and cetuximab versus the same regimen plus VTX-2337 in the first-line setting for SCHNN patients (NCT01836029).

Oncolytic Virus Therapy

Oncolytic viruses exploit the ability of a viral infection to target specific

cells. Viral therapy can induce cell lysis of infected cells and an acute vascular disrupting effect or provoke antitumor immunity.[228] Reolysin is a proprietary variant of a reovirus, an acronym for respiratory enteric orphan virus, based on phase I/II results demonstrating tolerability and activity in advanced solid malignancies.[229] Reolysin is being evaluated in a double-blind phase III study in combination with paclitaxel and carboplatin in platinum-refractory SCCHN (NCT01166542). Despite a preliminary press release[230] from the company indicating that in an intent-to-treat analysis, there was promising improvement in PFS for the experimental versus the control arm (p = 0.0072, HR = 0.5360); confirmatory data, overall survival endpoints, and trial details have not been released or published to date. A genetically modified adenovirus, Onyx-015, was evaluated in a phase III clinical trial, which did not show any improvement in overall survival, halting its development in the United States.[231] A similar virus, H101, has been approved by regulatory agencies in China for the treatment of SCCHN. The approval was based on a phase III trial, with a 79% response rate in patients receiving H101 by intratumoral administration in combination with cisplatin and 5-fluorouracil (5FU); however, its effect on survival is unknown.[41] The development of a new version of H101, H103, including a heat shock protein designed to attack metastatic tumors, is currently under way.[231]

Antibodies Inhibiting Cytokines

Hepatocyte Growth Factor/c-MET Pathway.

The secretion of HGF promotes tumor growth and metastases through c-MET signaling and inhibition of dendritic cell maturation.[232] The HGF/c-MET pathway is expressed and up-regulated in SCCHN,[122] and its activation leads to resistance to both chemotherapy and radiation.[233,234] Ficlatuzumab and rilotumumab are antibodies against the HGF that are in different stage of development against a variety of malignancies. Protocols to study them in SCCHN patients are currently in development.[235]

TGF-Beta.

TGF-beta is found to be significantly elevated in the serum of patients with HPV-negative SCCHN. In a xenograft model, the addition of an antibody

against TGF-beta with cetuximab improved antitumor efficacy when compared to treatment with cetuximab alone. Fresolimumab is an antibody against TGF-beta currently in development that could potentially be beneficial for SCCHN patients.

Immune-Stimulating Agonistic Antibodies.

For T-cell stimulation and activation, there are a number of accessory surface costimulatory receptors that are involved in the priming of the immune system, cytolysis, and memory cell differentiation. Agonistic antibodies to a number of costimulatory T-cell receptors such as CD40, OX40, and CD137 are in early-phase clinical trials and may have activity in SCCHN. These antibodies could also be additive or synergistic with chemotherapy, radiation, other targeted antibodies, and other immunotherapies, including the immune checkpoint inhibitors. The binding of CD40 to its ligand on activated CD4+ T cells can enhance antigen-presenting cell priming, secrete immunostimulatory cytokines, and up-regulate antigen-processing and cytotoxic T-lymphocyte priming. A patient with refractory SCHNN demonstrated a long-term complete response in a phase I trial of a recombinant CD40 ligand agonist.[236] This pathway seems to be actively involved in SCCHN immune evasion and merits further exploration and development in SCCHN.

OX40 signaling is involved in the survival, expansion, and memory of T helper cells and stimulating inflammatory cytokine production and decreasing suppression by T regulatory cells.[237] Patients with SCCHN have lower levels of circulating T cells that express OX40 and CD137 compared to controls.[238] OX40 antibodies have demonstrated antitumor activity in a number of solid tumor preclinical models. A phase I study in a select number of solid tumors including SCCHN is currently under way (NCT02221960). CD137 also has immunostimulatory attributes, and activation on NK cells helps enhance the ADCC effect of cetuximab and NK cell–mediated direct cytotoxicity. Preclinically, cetuximab induces CD137 up-regulation on NK and enhances its cytolytic activity in SCCHN models.[239]

Antibodies against Immune Checkpoints

To prevent autoimmune reaction and to protect healthy tissues when the immune system is activated, T cell activation is highly regulated, and several inhibitory pathways are expressed in immune cells. Cancer takes advantage

of this inhibitory signaling to prevent T-cell activation and escape the immune response.

Cytotoxic T-lymphocyte A-4 (CTLA-4).

The recognition of antigens presented by the major histocompatibility complex is not enough to turn on a T-cell response, and a second signal delivered by the B7 costimulatory receptor is required. When B7 binds to CD28, it provides an activating signal. In contrast, if it binds to CTLA-4, an inhibitory signal is provided. Ipilimumab and tremelimumab are antibodies that inhibit the CTLA-4 inhibitory signaling. Ipilimumab is FDA approved for the treatment of metastatic melanoma due to its benefits on overall survival.[240] An ongoing phase I trial at the University of Pittsburgh is exploring 3 courses of ipilimumab after treatment with cetuximab and intensity-modulated radiation therapy (IMRT) for SCHNN patients with high- or intermediate-risk AJCC stage III/IV (excluding T1N1) cancer of the oropharynx, hypopharynx, and larynx for tolerability and potential efficacy (NCT01935921).

Programmed Death 1 Checkpoint Blockade.

Programmed death 1 (PD-1) can be expressed by T cells, B cells, and myeloid dendritic cells (DC). It is highly expressed in T-regs, which are commonly found to be infiltrating tumors and may contribute to suppressing effector immune responses.[241] Its ligand (PD-L1) is inducible and constitutively expressed in several malignancies including SCCHN.[210] Interactions between PD-1 and PD-L1 in the tumor microenvironment lead to inhibition of the immune response against the tumor through several mechanisms including the inhibition of effector T cells, the induction of tolerance mediated by T-regs,[242] and the activation of an antiapoptotic pathway signaling (**Fig. 32.1**).[243]

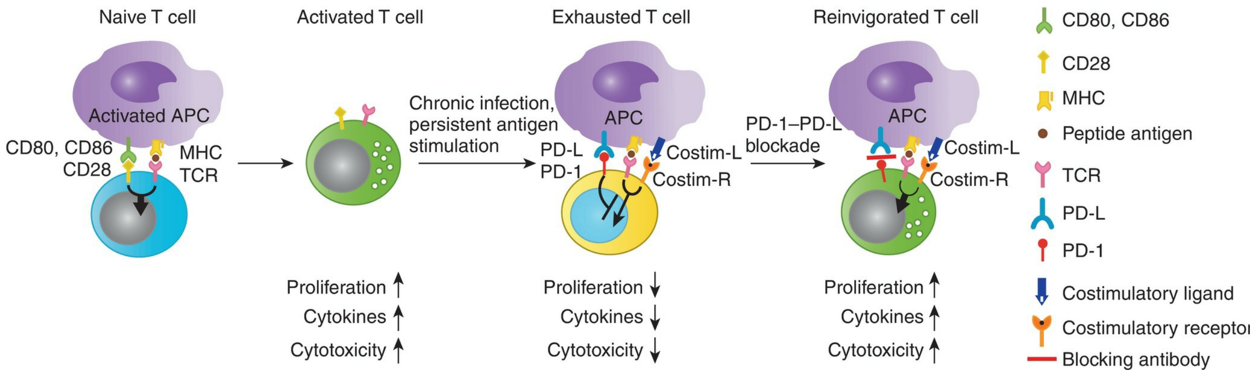

Figure 32.1. PD-1 and PD-L1 blockade—a strategy for immunotherapy in SCCHN. (Adapted and modified from Sharpe AH, et al. *Nat Immunol*. 2007;8:239.)

PD-L1 is frequently expressed in SCCHN. Three sets of retrospective case series have established that PD-L1 expression is more commonly found in HPV-related than in HPV-negative SCCHN: 62.5% versus 40%,[244] 49.2% versus 34.1%,[245] and 70% versus 29%.[246] This increase in PD-L1 expression contributes to a local immune resistance that allows HPV to infect and may contribute to the malignant transformation process.[246] Studies of various malignancies have been discordant in terms of correlation of expression of PD-L1 and prognosis,[241] and the same is true for SCCHN.[244,247,248] These differences may be methodologic in that PD-L1 measurement has not been standardized (different antibodies, different cutoff levels for positivity, and different definitions of positivity whether it be on tumor cells, stroma, or tumor-infiltrating cells). Additionally, the expression of PD-1/PD-L1 may be dynamic and fluid through time, subject to changes in the microenvironment, and even potentially up-regulated with therapy.[210]

Treatment with anti-PD-1 and anti-PD-L1 monoclonal antibodies in phase I trials initially included multiple solid tumor types and demonstrated unprecedented durable tumor responses.[212] Currently, a number of different anti-PD-1 and anti-PD-L1 antibodies are being developed (**Table 32.1**). As most of the reported data have been in early-phase studies, the differences between anti-PD-1 and anti-PD-L1 agents or the use of IgG1 or IgG4 backbones have not been elucidated. Moreover, different agents may have different efficacy and tolerability in different tumor types. It is important to note some theoretical differences. PD-L1 inhibition only inhibits the binding of PD-L1 to PD-1; in contrast, antibodies against PD-1 inhibit both PD-L1

and PD-L2 signaling. This subtle difference could translate into increased toxicity for anti-PD-1 therapy as both PD-L1 and PD-L2 have been implicated in playing an important role in maintaining immune homeostasis. Another theoretical difference is that targeting PD-1 can saturate this T-cell receptor in the periphery, which obviates the need for antibody penetration into sites such as the CNS.[249]

Table 32.1 Seven Companies Developing PD-1 Checkpoint Inhibitors

Anti-PD-1 Antibodies			
Nivolumab	Bristol-Myers Squibb	IgG4	Phase 3
MK-3475	Merck & Co	IgG4 (humanized)	Phase 3
Pidilizumab	CureTech	IgG1 (humanized)	Phase 2
AMP-224	AstraZeneca/MedImmune	PD-1/B7 Fc fusion protein	Phase I
AMP-514		IgG	Phase I
	Novartis (CoStim)	IgG	Phase I
Anti-PD-L1 Antibodies			
MPDL3280A	Genentech/Roche	IgG1	Phase 3
MEDI-4736	AstraZeneca/MedImmune	IgG1	Phase 2
MSB0010718C	EMD Serono (Merck KGa)	IgG	Phase 1

www.clinicaltrials.gov, Accessed May 12, 2014.

In SCCHN, several clinical trials have been ongoing with some preliminary findings reported. In a phase Ib study of pembrolizumab, MK-3475, an antibody designed to block the PD-1 interaction with its ligands PD-L1 and PD-L2, patients with recurrent or metastatic SCCHN that were positive for expression of PD-L1 (1% on tumor cells or stromal cells) were treated. Of 104 patients screened for PD-L1 positivity, 81 (78%) were positive of which 60 received ≥1 dose. A preliminary analysis showed that the drug was well tolerated and had an overall response rate of 20% (n = 11/56 evaluable patients) with a response duration that ranged from 8+ to 41+ weeks (median had not been reached).[250] Preliminary results of the anti-PD-L1 antibody, MEDI4736, also demonstrated durable responses in 14% (n = 4/29) of recurrent or metastatic SCCHN patients.[251] Currently, seven different companies have inhibitors of PD-1 or PD-L1 that are being tested in phase I to III clinical trials for a variety of malignancies.

The use of PD-L1 as a predictive biomarker to determine who will respond or should be treated with immunotherapy is not well established. In melanoma, NSCLC, and other solid tumors, patients with stronger expression

of PD-L1 tend to have higher response rates to these agents; however, responses and clinical benefit have been seen in patients whose tumors are negative for PD-L1 expression.[252] Therefore, development of predictive biomarkers is likely to be more complex than PD-L1 positivity alone. Gene arrays, tissue immune infiltration scores, and peripheral immunologic markers are being explored.

What is notable about the PD-1/PD-L1 inhibitors is the highly tolerable toxicity profile that enables long-term administration. Mild toxicities such as fatigue, pruritus, rash, and infusion reactions have been commonly observed. In SCCHN, the rate of reported adverse events ranges from 39% to 58%, the majority of them being grade 2 or less,[250,251] whereas severe toxicities are infrequent and, in contrast to the experience with CTLA-4 blockade, immune-related toxicities are rare.

The immune-related toxicities experienced with the CTLA-4 and PD-1/PD-L1 inhibitors appear to occur more frequently in responding patients and range in severity from mild to fatal, generally appearing late, 8 to 10 weeks after initiation of therapy. Toxicities can also be long lasting, even months after discontinuation of therapy, and may even potentially affect the toxicity profile of subsequent therapies. Most adverse events that are considered immune adverse events can generally be treated with steroids and immunosuppressants with resolution.[253] Despite their rare incidence, immune-related toxicities with the PD-1 checkpoint inhibitors can affect any organ system, and toxicities of diarrhea, rash, liver enzyme changes, endocrine abnormalities, renal dysfunction, and musculoskeletal abnormalities have been reported. Early detection and management are important to avoid severe consequences. Algorithms for the management of toxicity have been established for the CTLA-4 inhibitor, ipilimumab, in melanoma; the toxicity management of the PD-1 checkpoint inhibitors is still in evolution and has yet to be fully defined. The sensitivity and tolerability to immune checkpoint inhibitor toxicity may vary in different solid tumor populations, especially in SCCHN patients who may have smoking- or alcohol-related comorbidities.

Cell-Based Therapies

T-cell therapies involve the harvesting of a patient’s own tumor antigen-specific cells followed by different types of manipulation in vitro with the

goal of priming them prior to reintroduction into the patient. This is a complex and laborious methodology; however, impressive results have been reported in several tumors, including a complete response in a patient with SCCHN.[254] In HPV-related tumors, T cells specific against the HPV antigens E6/E7 have been expanded in vitro, and a recent reported trial in patients with refractory cervical cancer showed one partial response and two complete responses.[255] This strategy is currently being tested in an ongoing phase II study of HPV-positive cancers, including HPV-positive SCCHN (NCT01585428).

Defining Mechanisms of Resistance to Immunotherapy

Although promising results have been seen in SCCHN, most patients do not respond to immunotherapy and those who do eventually acquire resistance and tumor growth. In the case of immune checkpoint inhibition, rechallenging patients with the same therapy after an initial response can reinduce tumor regression, but it does not do so consistently in all patients.[256,257] Another strategy in nonresponders or patients that progress is to induce response and an inflammatory tumor milieu with infiltrating T cells via the use of combination strategies—either sequential or concurrent with chemotherapy, radiation therapy, targeted therapies, or other immunotherapies. These approaches are being explored in early-phase trials, and their efficacy and toxicity, optimal administration, and sequencing are yet not determined. Several ongoing clinical trials are combining forms of immunotherapy such as the use of cancer vaccines along with checkpoint inhibitors and the use of costimulatory T-cell receptors and CTLA-4 antibodies (**Fig. 32.2**).[258]

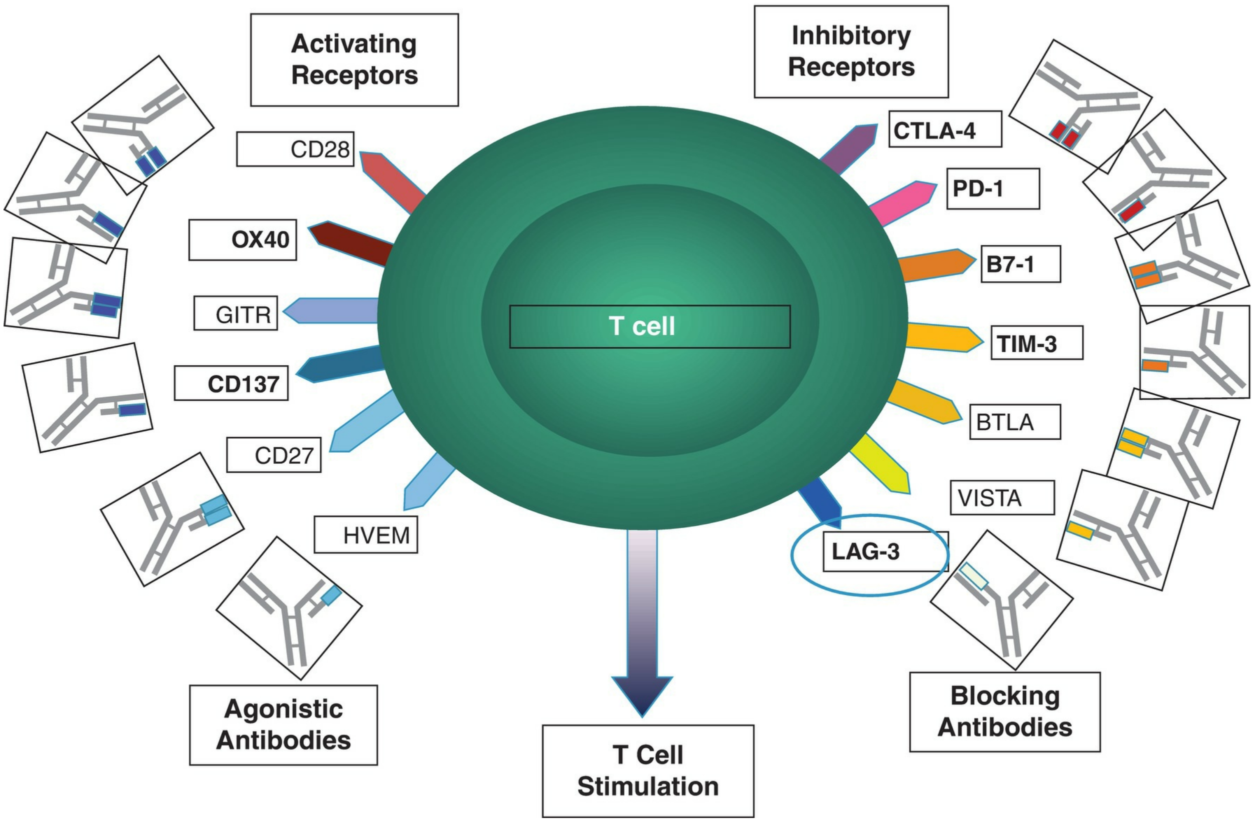

Figure 32.2. T-cell immune checkpoints as targets for immunotherapy. (Adapted and modified from Mellman I, et al. *Nature*. 2011;480:480–489.)

Interaction of Targeted Therapies with Radiation for SCCHN

Radiation therapy is a cornerstone of multidisciplinary care in patients with SCCHN, especially those with locally advanced disease. Therefore, targeted therapies are often studied in the context of radiation therapy or for their radiosensitizing properties. EGFR inhibitors and radiation therapy were discussed in detail elsewhere in this chapter, but multiple other agents have been investigated in SCCHN although the only approved targeted agent thus far is cetuximab.

Angiogenesis

The molecular mechanism through which HPV mediates tumor angiogenesis has been well established. The HPV virus integrates into host DNA and the E2 reading frame is disrupted leading to lack of repression of E6 and E7. E6 inactivates tumor suppressor protein p53. Decreased p53 causes subsequent

up-regulation of TSP-1 and VEGF. E7 inactivates tumor suppressor protein Rb. VEGF is then in turn up-regulated by HIF-1-alpha, which leads to angiogenesis. Macroscopically, abnormal vascular markings can be easily seen during direct laryngoscopy in patients with invasive SCCHN.

Bevacizumab is a recombinant monoclonal antibody that inhibits VEGF, which is responsible for angiogenesis. Ferrara's laboratory was the first to isolate and sequence VEGF.[259–261] In 1993, Ferrara reported that a mouse anti–human VEGF monoclonal antibody inhibited the growth of several tumor cell lines in nude mice.[259–261] In 1997, the anti-VEGF antibody was humanized and Genentech initiated the first phase I trials. A phase III trial of bevacizumab in addition to 5FU chemotherapy in metastatic colorectal cancer conferred a statistically significant overall survival benefit and led to FDA approval in 2004.[262] Since then, bevacizumab has had great clinical success in a wide range of different tumor types. Bevacizumab has been tested in combination with radiation. Willett et al.[263] established the safety of bevacizumab in patients with locally advanced rectal cancer who received combination of chemoradiation.

Given the relationship between HPV and angiogenesis, it is natural to imagine that bevacizumab would play a role in SCCHN. RTOG 0615 examined the use of bevacizumab concurrently with radiation and cisplatin in a phase II trial of patients with nasopharyngeal carcinoma. The addition of bevacizumab to standard chemoradiation treatment for patients with nasopharyngeal cancer showed feasibility and potentially might delay the progression of subclinical distant disease.[264] Interestingly, nasopharyngeal cancer is known to be caused by Epstein-Barr virus (EBV) rather than HPV, so the molecular mechanism for which EBV and angiogenesis are related is unclear.

Oncolytic Viruses

Preclinical literature supports the hypothesis that oncolytic viruses are effective in treating SCCHN.[265] Oncolytic viruses have synergistic effects with chemoradiation therapy.[266] In particular, vaccinia has shown efficacy above other poxviruses specifically in SCCHN.[267]

GLV-1h68 is a genetically modified, attenuated form of recombinant vaccinia that has been intensively investigated in HNC. Preclinical studies

show that GLV-1h68 infects and lyses HNSCC in vitro and in vivo.[268] Mansfield et al. have shown that cell killing by GLV-1h68 is dose and time dependent, with infectivity increasing in S-phase and sub-G1 cells.[266] In addition, radiation augments vaccinia-mediated cell death, apoptosis, and tumor xenograft regression.[266] A phase I trial in previously untreated stage III to IVB head/neck cancer at UC San Diego has found that intravenous GL-ONC1 is safe and well tolerated when delivered concurrently with radical chemoradiation therapy at radiation doses of 70 Gy and cisplatin 100 mg/m^2 delivered triweekly. Currently, there is a phase I trial of attenuated vaccinia virus delivered intravenously with concurrent cisplatin and radiation therapy in patients with locoregionally advanced SCCHN.

Histone Deacetylase Inhibitors

Histone deacetylase (HDAC) inhibitors are becoming important antineoplastic agents, which have been observed to alter transcription, differentiation, cell cycle, and apoptosis. Recent preclinical studies suggest that they have an important role in radiosensitization.[269] De Schutter et al.[270] investigated the use of HDAC inhibitors in SCCHN and found radiosensitizing doses induced histone hyperacetylation and reversal of gene silencing and increased radiation-induced cell cycle arrest. CUDC-101 is a multitargeted agent designed to inhibit EGFR, HER2, and HDAC and was tested in a phase I dose escalation study in patients with locally advanced head and neck cancer showing preliminary evidence of antitumor activity and was well tolerated.[271]

mTOR Inhibitors

Preclinical studies have shown that everolimus and other mTOR inhibitors increase efficacy of cisplatin in cancer cell lines. Everolimus has been tested in a phase 1 study with cisplatin and IMRT for head and neck cancer and was shown to be both safe at therapeutic doses of 5 mg/day.[272]

PI3K Pathway Inhibitors

Rigosertib has been shown to inhibit the PI3K pathway in many different cell lines.[273] PIK3CA alterations have been shown in SCCHN (see above). A current phase I study is testing whether rigosertib when added to

chemoradiation will improve PFS in patients with HPV-positive intermediate– or high–risk SCCHN. Preliminary data show promising activity and minimal toxicity.[273] A phase II study is currently under way in the metastatic setting.

Ras/Raf/MEK/MAPK Inhibitors

Sorafenib is a small molecule inhibitor of multiple different tyrosine kinases including Raf, VEGFR, and PDGFR and induces autophagy. In 2006, the FDA-approved sorafenib for advanced renal cancer and then for hepatocellular carcinoma in 2007. Sorafenib has been shown to sensitize SCCHN to ionizing radiation in preclinical studies.[39] Sorafenib is thought to sensitize tumor cells to chemoradiation therapy by down-regulating DNA repair proteins ERCC-1 and XRCC-1 as well as blocking angiogenesis.[274]

Immunotherapies

Preclinical models of radiation and anti-PD-1 antibodies have been shown to suppress tumor growth at both radiated and nonradiated sites and enhance the radiation therapy-induced abscopal effect.[275] The biologic mechanism for this abscopal effect is thought to be due to radiation inducing antigen-specific immune responses. In a mouse model, radiation therapy altered the immunophenotype of tumor cells and increased antigen presentation resulting in increased primary tumor control and abscopal effects outside of the radiation field.[276] The RTOG is currently developing an upfront phase II trial of cisplatin with or without nivolumab or cetuximab with or without nivolumab in intermediate-/high-risk HNSCC.

The evolution of molecularly targeted therapy in SCCHN has been rapid. Just in the last decade, we have witnessed the approval of an EGFR-directed antibody, cetuximab, and a tremendous increase in the understanding of SCCHN biology. There are currently several agents in phase III testing covering a plethora of drugs and mechanisms. The hope of all these trials is to improve long-term outcomes and cure rates in this disease.

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33 Rehabilitation of Swallowing and Speech in Patients Treated for Cancer of the Head and Neck

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INTRODUCTION

Unlike past decades in which functional rehabilitation of speech and swallowing was often considered an afterthought once definitive treatment of the head and neck cancer was completed, functional preservation, that is, the ability to eat, drink, and speak normally, shares a primary goal with cure and survival in the contemporary management of patients with cancer of the head and neck. Patients who were once satisfied if not grateful to be cured of their cancer, whether or not they could eat or speak, currently expect that verbal communication and the ability to swallow without aspirating will remain intact after treatment, with a spontaneous ability to return to a normal daily routine once they have recovered from treatment. Unfortunately, as organ-sparing treatment alternatives for head and neck cancer have intensified, and their ability to cure the disease has improved, the short and long-term effects on speech and swallowing have become even more severe. Treatment regimens have become stronger, frequently combining surgical and nonsurgical alternatives, given in regimens and doses that often result in significant anatomical defects, severe fibrosis, and long-term neuropathies that can cause irreversible damage to the upper aerodigestive tract (UADT), that in some instances, relegate the patient to a tracheostomy and gastrostomy tube dependence.

The diagnosis of cancer of the head and neck, the tumor itself, and the consequences of its treatment can impart a tremendous impact on the individual’s physical, physiologic, psychological, and social functioning. The

diagnosis itself will almost certainly be associated with concerns regarding body image, self-concept, self-esteem, and the ability to return to work and social interactions. However, in all cases, cancers of the head and neck will, to some degree, affect speech and swallowing function that will require accurate evaluation and targeted rehabilitation from clinicians with critical expertise and experience managing patients with cancer of the head and neck. Pretreatment evaluation and counseling and posttreatment intervention must be timely and precise to optimize patient outcomes and successful recovery. Hence, treatment based on limited knowledge and inaccurate interpretation of evaluations remains ineffective and useless.

Over the past two decades, there has been a paradigm shift away from ablative surgery to organ preservation with an associated emphasis on quality of life, function, and the cost of treatment. For patients with early cancer of the larynx, the treatment dichotomy generally remains a decision to use laser excision of the cancer or to treat with radiation therapy. For patients with advanced cancer of the larynx, the contemporary focus is also to preserve the larynx. Unfortunately, elevated rates of speech and swallowing dysfunction prevail. Hence, in some cases, questions have arisen as to the true benefit of organ preservation versus total organ resection using contemporary surgical–prosthetic methods of voice restoration and early swallowing exercise regimens to maintain acceptable oral communication and prevent long-term dysphagia.

Likewise, for patients with cancer of the oropharynx, the question regarding the optimal treatment alternative also continues to be investigated and debated. Today’s patient with cancer of the oropharynx is generally younger than his or her older counterpart, often in the fourth or fifth decade of life, with a better prognosis for survival, and is adamant about the ability to return to a normal routine of work and social activities after treatment. Thus, posttreatment morbidity and function have become primary considerations in decisions regarding the contemporary treatment of cancer of the oropharynx. Despite ongoing investigation, the clear advantage of new endoscopic surgeries (eHNSs) of the head and neck using laser and robotic resections versus nonsurgical alternatives that use intensity-modulated radiation therapy (IMRT) with photon or proton beams, or adaptive radiation protocols, to preserve function, is still being investigated.

What we have learned over the past several decades is that patients’ goals

have not changed significantly; their posttreatment expectations continue to be able to eat and swallow by mouth, to speak using their natural laryngeal voice, and to keep their appearance unchanged. Patients' self-perception of their ability to eat and drink is often inaccurate and incongruous with the findings seen on instrumental tests; that is, what is seen on objective examination does not always corroborate the patients report. Experience and investigation have demonstrated that in patients who have been treated with radiation therapy, severe dysfunction, primarily dysphagia, often occurs late, years after the cancer treatment has ended, and is most often refractory to current standard methods of behavioral dysphagia therapy. Likewise, high rates of aspiration that are often silent (without patient awareness) and result in aspiration pneumonia and chronic gastrostomy tube dependence remain common occurrences and are also associated with elevated rates of dysphonia and vocal fold paralysis particularly after surgical treatment for cancers of the head and neck. Finally, data demonstrate that anatomical preservation does not ensure functional preservation nor is the potential for recovery a guarantee for successful functional results. Likewise, outcomes will vary in terms of both the response to the cancer treatment as well as the long-term speech and swallowing results. Thus, the exact predictors of functional outcomes still remain unknown.

Normal Speech and Swallowing Function

Speech and swallowing are highly complex processes that depend on a series of neuromuscular events that rely on rapid, highly coordinated, and precisely executed movement. The sequence of the motor events involved in both speech and swallowing is fairly predictable, although in the case of swallowing, investigators have shown that the relative timing of these events varies, depending on the size and consistency of the bolus of food or liquid being swallowed.[1–3] In general, speech production is affected primarily by cancers that involve the oral tongue or other structures of the oral cavity, whereas swallowing can be affected by any cancer within the aerodigestive tract. However, in most instances, the greatest impact on swallowing occurs from tumors that affect the base of the tongue or pharynx.[4]

Speech production and intelligibility depend on precise sequences of movement and contact by the articulators of the oral cavity, mainly the lips, tongue, and soft palate, that rapidly change the configuration of the vocal

tract. Although articulation is the main contributor to speech intelligibility, speech understandability is also influenced by voice quality and resonance. Hence, any cancer that affects structures other than the tongue, such as those that impact the larynx, specifically vocal fold function, or fill the recesses of the naso-, oro-, or laryngopharynx, will result in changes in the quality of the voice (loudness, pitch, resonance) and also indirectly influence speech intelligibility. The place of articulatory contact may be bilabial (m, p, and b) or it may be velar (k and g). Whether the sound is nasal or voiced depends on the valving action from the velum, which requires a lowering of the soft palate for nasal sounds (m, n, and ng) or valving from the larynx that involves the opening or closing of the vocal folds to produce the voiced distinction between various sounds (p and b, t and d, k and g). In the case of vowels, the shape and height of the tongue are the key determinants of sound distinction. Thus, a cancer that involves the oral cavity, pharynx, or larynx will have some effect on speech and voice production and ultimately on conversational intelligibility.

The act of swallowing can be divided into four unique stages, the oral preparatory, oral, pharyngeal, and esophageal phases that involve more than 30 pairs of muscles and six cranial nerves. Each of these stages depends on intact neurologic function and anatomy with the triggering of each successive stage dependent on the timely occurrence of the previous one. Variations in normal anatomy that affect size, shape, or symmetry have little significant impact on swallowing in healthy individuals but may result in impaired swallowing or further decompensation including aspiration in an otherwise debilitated patient.[5] In general, the oropharyngeal swallow begins at the lips and ends as the bolus enters the cervical esophagus at the level of the cricopharyngeal inlet and involves both voluntary and involuntary control mechanisms, and the entire oropharyngeal swallow should take no longer than 1 to 2 seconds in normal individuals.[6] Only the oral preparatory, oral, and pharyngeal stages can be addressed by behavioral therapies, as the esophagus is a relatively less complex muscular tube, for which the main therapeutic maneuver is dilation. Although the gastrointestinal radiologist and the speech pathologist work together to diagnose abnormalities associated with swallowing function, diagnosis of abnormalities associated with the esophageal stage of swallowing remains the responsibility of the diagnostic radiologist.

Risk and Predictors of Dysfunction

Tumor site and extent and treatment intensity are the key clinical predictors of functional outcomes after organ preservation.[7] Data demonstrate that among cancer sites treated with radiation or chemoradiation regimens, cancers of the hypopharynx portend the worst functional outcomes. Both cancer of the hypopharynx and combined regimens of chemotherapy and radiation are associated with the highest rates of swallowing-related dysfunction including dysphagia, stricture, and pneumonia when compared to other cancer sites such as the tongue, larynx, and oropharynx or single-modality treatments or a combination of surgery and radiation therapy.[8] Although data suggest that the staging of the primary cancer of the head and neck carries a prognostic significance per TNM criteria, T stage appears to be the most consistent staging variable that impacts long-term function, often predicting the severity of dysphagia, gastrostomy dependence, and aspiration after treatment of cancer of the head and neck. Oropharyngeal primary cancers have the second highest risk of dysphagia after treatment. A 39% to 64% prevalence of long-term dysphagia has been documented in patients with cancer of the head and neck treated with combined regimens of chemotherapy and radiation.[8,9]

Changes in voice remain the primary complaint in more than 75% of patients treated for early laryngeal disease (T1-T2) regardless of the treatment modality, and although subjective reports of long-term vocal outcomes are generally comparable, better acoustic and perceptual measurements have been reported in patients treated with radiation therapy.[10] Swallowing is generally not a complaint of patients treated for early cancer with a similar reported quality of life for both groups. However, the increased financial impact for patients treated with radiation therapy and the patient burden of missed work hours, travel time and distance, and the number of hours associated with treatment delivery are often concerns of patients selected to receive radiation therapy, in favor of surgical alternatives such as endoscopic laser procedures.

For patients with early cancer of the larynx who have been treated with radiation therapy, a continued history of smoking after completion of treatment has been shown to be associated with lower fundamental frequency changes in the voice and poorer vocal quality when compared with results in

nonsmokers.[11] Cancers that affect the anterior commissure generally result in patient complaints related to weak, breathy vocal quality and problems with pitch variation similar to the complaints of patients who have received larger volumes and doses of radiation (>60 Gy).[12] In contrast, superficial cancers of the true vocal folds have been shown to result in better vocal outcomes after laser resection than do cancers that are deeply invasive into the muscle of the true vocal fold. Large bulky cancers that invade the vocal fold or involve the anterior commissure put the patient at risk for poor vocal quality that is often weak in intensity and breathy in quality because of the large postoperative glottic defect that results in glottic incompetency for voice production. Unfortunately, there are few options for vocal improvement, behavioral or surgical, in these instances, and practice has shown that patients often experience better vocal outcomes after radiation therapy in lieu of a large defect that limits the ability to compensate or restore the voice after resection. Our anecdotal experience suggests that most patients still remain more willing to accept a poor voice in favor of the decreased patient burden associated with laser resection.

Alternatively, patients with advanced (T3-T4) cancer will experience greater and more severe functional debilitation particularly after organ preservation. More than 90% of patients will complain of dysphonia, of which ~25% will report severe vocal disabilities. Up to 10% mortality rates associated with aspiration pneumonia have been reported in treated patients with advanced cancers of the head and neck.[13] Late-occurring dysphagia and aspiration remain common with reported rates of silent aspiration as high as 70% in patients who aspirate[14,15] and rates of percutaneous gastrostomy (PEG) tube placement between 70% and 80% with long-term dependence >12 months between 5% and 15%.[7] Unfortunately, early recovery of swallowing may be misleading because of the delayed fibrosis and neuropathy that can eventually result in laryngopharyngeal dysfunction inhibiting the ability to swallow by mouth.

The cancer-related risk factors for long-term swallowing dysfunction generally have included advanced T stage, primary cancers that involve more than 50% of the base of tongue,[9,16,17] cancers that involve the tonsil and extend to the pharyngeal wall, and cancers with advanced cervical lymph node metastases. Patients who are nutritionally compromised and who demonstrate pretreatment changes in diet, G-tube placement, weight loss, or

malnutrition are at significant risk for long-term dysphagia. In addition, patients with persistent or recurrent cancer who require salvage procedures such as surgery or who present with comorbid diseases such as chronic obstructive pulmonary disease (COPD), diabetes, neuromuscular degenerative disease, substance abuse, or continued smoking, among others, also remain at high risk for poorer swallowing outcomes.

We are just beginning to understand the risk factors associated with long-term dysphagia after radiation or chemoradiation treatment. Studies have demonstrated that patients who have difficulty swallowing before treatment are also at higher risk for chronic dysphagia and permanent feeding tube dependency.[18] Likewise, prolonged intervals of nothing per oral (NPO) longer than 2 weeks during radiation or chemoradiation treatment are associated with poorer swallowing outcomes.[19] Therefore, it is important that patients are encouraged to eat and swallow as much as possible throughout the course of treatment, and even brief periods of NPO should be avoided.[20]

Finally, the viewpoint and preferences of the patient and the support of family and friends are essential components of treatment acceptance and compliance and ultimately long-term functional success. The psychological/psychosocial characteristics such as patient attitude, the attitude of the physician, particularly the surgeon, and the speech pathologist, and the attitude/support of the spouse or significant other have been found to be strongly related to successful functional outcomes. When the views of important others are nonsupportive, patients are less likely to achieve successful outcomes because of the detrimental effect on patient motivation, treatment adherence, and encouragement.[21–23]

The Interdisciplinary Team

Patients with cancer of the head and neck face multiple, often severe functional and psychological challenges associated with the diagnosis and treatment of their disease. Successful treatment for cancer of the head and neck and posttreatment rehabilitation depend on a strong, collegial interdisciplinary team for management. This is a point that cannot be overemphasized. Pretreatment evaluation and planning for functional rehabilitation should begin immediately after diagnosis and involve the entire oncologic care and rehabilitative team. After assessment and diagnosis by the

surgeon, the patient should, at minimum, meet with the radiation oncologist, medical oncologist, dentist or maxillofacial prosthodontist, speech pathologist, nurse, dietitian, and social worker. Specialists from other disciplines such as physical therapists and psychologists, among others, may also be needed and should be called to help when indicated. In particular, the need for speech and swallowing therapy is often an unexpected recommendation that both the patient and family frequently find difficult to accept because the ability to speak and swallow after treatment is commonly anticipated to be regained automatically without need for intervention. Experience has shown that recovery and rehabilitation are optimized when there is ongoing dialogue between all members of the interdisciplinary team and information is similarly provided to the patient by all members of the group.

Evaluation

Standardized functional assessments remain a critical component of comprehensive patient care and outcomes research. Pretreatment examination should establish a baseline for treatment planning and later posttreatment comparison. Baseline evaluation is critical because it documents pretreatment function and often is helpful in predicting long-term outcomes. A complete functional examination includes clinical assessment that depends on clinician appraisal during physical examination, such as the bedside swallowing examination, cranial nerve examination, and oral motor assessment among others. Clinician-driven examinations also include instrumental and imaging studies, as well as clinician-rated scales. In addition, a comprehensive functional examination must also recognize patient perception and therefore include patient-reported outcomes (PROs) such as quality-of-life questionnaires and symptom performance inventories.

Rehabilitation, and even more important, rehabilitative planning, should begin at the time of cancer diagnosis with patient counseling and a thorough baseline evaluation provided by a speech pathologist who is an expert in the evaluation and treatment of functional disorders associated with head and neck malignancies and their treatment. Baseline swallowing evaluation that includes instrumental examination, such as the modified barium swallow (MBS) study or flexible endoscopic evaluation of swallowing (FEES), documents important functional elements such as the presence of aspiration

and airway protection that have been found to be strongly predictive of long-term swallowing dysfunction. Aspiration, vocal fold paresis, feeding tube dependence, and tracheostomy prior to treatment have been reported as adverse prognostic indicators of posttreatment functional recovery.[7] Moreover, aspiration of thin liquids sufficient enough to necessitate dietary modifications before cancer treatment or an NPO status prior to beginning treatment significantly predicts swallowing dysfunction requiring NPO status in long-term laryngeal cancer survivors.[18] Additionally, it is important to determine the pretreatment effect of the cancer on swallowing as a decline in swallowing after radiation or chemoradiation treatment may not be related to fibrosis or posttreatment deconditioning but in fact may represent the loss of compensation for a cancer-related dysfunction once the cancer has been cured.

Most important is that pretreatment baseline assessment provides critical information in select patients for whom survival is comparable regardless of surgical or nonsurgical alternatives but whose function, swallowing and voice, may be improved with one of either modalities. Baseline evaluation also helps to identify those patients with pretreatment dysphagia or who are at significant risk for posttreatment swallowing dysfunction to ensure therapeutic placement of gastrostomy tubes as opposed to the common practice of prophylactically placing feeding tubes in all patients. Recent data indicate that patients with pretreatment dysphagia, whether self-reported or documented by instrumental evaluation, treated with radiation ± chemotherapy for cancer of the oropharynx, experience more frequent placement and longer gastrostomy tube duration beyond 6 months than do patients with adequate oral intake prior to treatment ($p < 0.001$).[24]

Finally, the results from baseline evaluation provided during patient counseling offer realistic posttreatment functional expectations that frequently facilitate patient understanding, acceptance, and compliance with both cancer and rehabilitative treatment recommendations. Baseline evaluation allows clinicians to assess outcomes and draw conclusions that cannot be determined without appropriate pretreatment functional examination. It is for these reasons, among others, that pretreatment referral to speech pathologists for baseline functional evaluation has been recognized as best practice for all patients particularly for patients treated with nonsurgical organ preservation.[25,26]

METHODS OF EVALUATION

Clinical/Bedside

The clinical evaluation is useful because it is based on observation in a more natural, relaxed environment that is often representative of actual patient routine. However, it is important to remember that clinical observation lacks the sensitivity of instrumental examination. The most common clinical assessment of swallowing is often referred to as the bedside examination. The bedside swallowing examination always precedes the instrumental (MBS, FEES) study. It provides a basic screening to identify patients who have a “functional” swallow and who do not require instrumental examination. The clinical examination also allows the clinician to help determine the timing or readiness to begin oral intake. Not all patients require instrumental examination as these tests are often expensive and impractical and are associated with a resource burden that can be avoided when clinical examinations are performed accurately and in a timely fashion.

The clinician should obtain a thorough case history and perform a comprehensive evaluation of motor speech functioning that allows the development of a hypothesis of swallowing competency and dysfunction related to neurologic functioning and patterns of movement. Again, clinical examinations provide important information that is critical to the patient’s functional status. However, it is important to remember that bedside observation of swallowing function cannot reliably determine or rule out silent aspiration. Nor can observation reliably diagnose pharyngeal swallowing disorders because the problems that occur during the pharyngeal stage of swallowing must be inferred by the clinician. Despite this limitation, the examiner can detect signs and symptoms suggestive of pharyngeal swallowing impairments during clinical observation and evaluation. The goal of the clinical examination is to synthesize the overt as well as the subtle observations and use this knowledge to make recommendations including the need for further, more objective swallowing assessment.

Patient-Reported Outcomes

A variety of assessments are available to assess both speech and swallowing that include both quality-of-life and symptom performance scales. Measures

of patient report rely on patient perception of functional status. Data, however, have shown that patients' report of their functional status is frequently unreliable and more often does not accurately reflect physiologic performance and actual abilities.[27] Patients frequently report normal swallowing despite abnormal findings of silent aspiration shown on MBS examination.[28,29] Conversely, patients also report abnormal swallowing function associated with radiation-induced xerostomia despite functional MBS findings. Several noninstrumental tools have been shown to be good indicators of functional status particularly in patients with cancer of the head and neck. The Performance Status Scale for Head and Neck (PSS-HN) assesses three areas, normalcy of diet, understandability of speech, and eating in public, and is a simple clinician-rated tool that can provide valuable indicators of both speech and swallowing function.[30] The MD Anderson Dysphagia Inventory (MDADI) is a 20-item patient-reported instrument, scored on a scale from 1 to 5, consisting of global, emotional, functional, and physical subscales that evaluate the effects of dysphagia on quality of life (QOL) from the patient's perspective.[31] Alternatively, the Functional Oral Intake Scale (FOIS)[32] is another simple, validated tool that helps quantify the functional status of the patient with regard to feeding tube dependence and level of oral intake.

In addition, a variety of assessments are available to evaluate vocal functioning. Among them are the Voice-Related Quality of Life (V-RQOL),[33] the Voice Symptom Scale (VoiSS),[34] and the Voice Handicap Index (VHI-30)[35] and its shortened version VHI-10.[36] The Consensus Auditory–Perceptual Evaluation of Voice (CAPE-V)[37] is a frequently used measure of voice perception that provides clinician-rated assessment of such vocal parameters as roughness, asthenia, breathiness, and strain.

Although there are multiple tools for assessing voice and swallowing function, there are relatively few assessments specifically designed for evaluation of speech intelligibility. The Speech Handicap Index has been validated for use in the head and neck population.[38,39] Although the Assessment of Intelligibility of Dysarthric Speech[40] has not been standardized for use in patients with cancer of the head and neck, it provides valuable information regarding articulation for therapeutic planning that is often beneficial for patients with cancer of the head and neck. In addition, the understandability of speech component of the PSS-HN provides a simple and

quick clinician-rated assessment of the intelligibility of speech production that is graded by a single score (0 never understandable to 100 always understandable).

The importance of patient experience and opinion as critical components of functional recovery and performance should not be disregarded. However, only instrumental examination, such as the MBS study or FEES, in the case of swallowing function, and direct observation of vocal fold function using endoscopy or stroboscopy, can provide physiologic information that ultimately identifies the etiology of dysfunction. Both anecdotal experience and research findings support the recognized discrepancy between patients' perception of their handicap versus instrumental evaluations that examine physiologic aspects of function. Therefore, comprehensive examination should include both the findings from PRO measures along with those from instrumental evaluations of speech and swallowing abilities to ensure accurate interpretation of functional status.

Modified Barium Swallow Study

The most widely used and likely still the gold standard of instrumental swallowing evaluations remains the MBS examination, also referred to as the videofluoroscopic assessment of swallowing. This is because the MBS study evaluates the entire oropharyngeal swallow, from the point at which the food passes the lips to the time it enters the cervical esophagus. The MBS study is performed jointly by a speech pathologist and a radiologist. The examination should be performed in standard fashion including the use of radiopaque liquids, pastes, and solid consistencies as swallowing physiology will vary depending on the consistency and the amount of food presented. The MBS study is the examination of choice for swallowing assessment versus the traditional barium swallow study or esophagram, the purpose of which is to evaluate the structural integrity of the pharyngoesophagus and identify aspiration during continuous swallowing of a large liquid bolus. Furthermore, the barium esophagram does not provide the information necessary to identify dysfunction of oropharyngeal swallowing nor do the results allow a differential diagnosis of the etiology of aspiration.

The primary purpose of the MBS examination is to understand oropharyngeal swallowing physiology as it relates to swallowing dysfunction. A number of important observations can be made from the MBS study that

include the presence of penetration of swallowed material into the laryngeal vestibule and the degree of aspiration into the trachea using the validated Penetration–Aspiration Scale.[41] The efficiency of the swallow can also be measured and quantified with the oropharyngeal swallowing efficiency (OPSE) score.[42] In addition, the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scale offers a novel grading schema that summarizes the interaction between swallow safety measured by penetration aspiration events and swallowing efficiency estimated by pharyngeal residue, in a psychometrically validated scale. One of the advantages of the MBS study is that the examiner can immediately assess the effectiveness of selected swallowing techniques and strategies to relieve the dysphagia during study administration.[43] Most important, videofluoroscopic findings during MBS examination document swallowing physiology, laryngeal sensation, and aspiration and have been reliably associated with health risk prediction rates particularly for pneumonia.[29]

Figure 33.1 shows a lateral radiographic view of normal oropharyngeal anatomy prior to swallow initiation during the MBS study. No evidence of aspiration or residue is seen following swallowing completion as shown in **Figure** 33.2. **Figure** 33.3 demonstrates aspiration associated with disordered swallowing function.

Figure 33.1. Lateral radiographic view of normal oropharyngeal anatomy seen during MBS examination.

Figure 33.2. Normal swallowing results during MBS examination. Note the lack of tracheal aspiration or oropharyngeal residue after the swallow is completed.

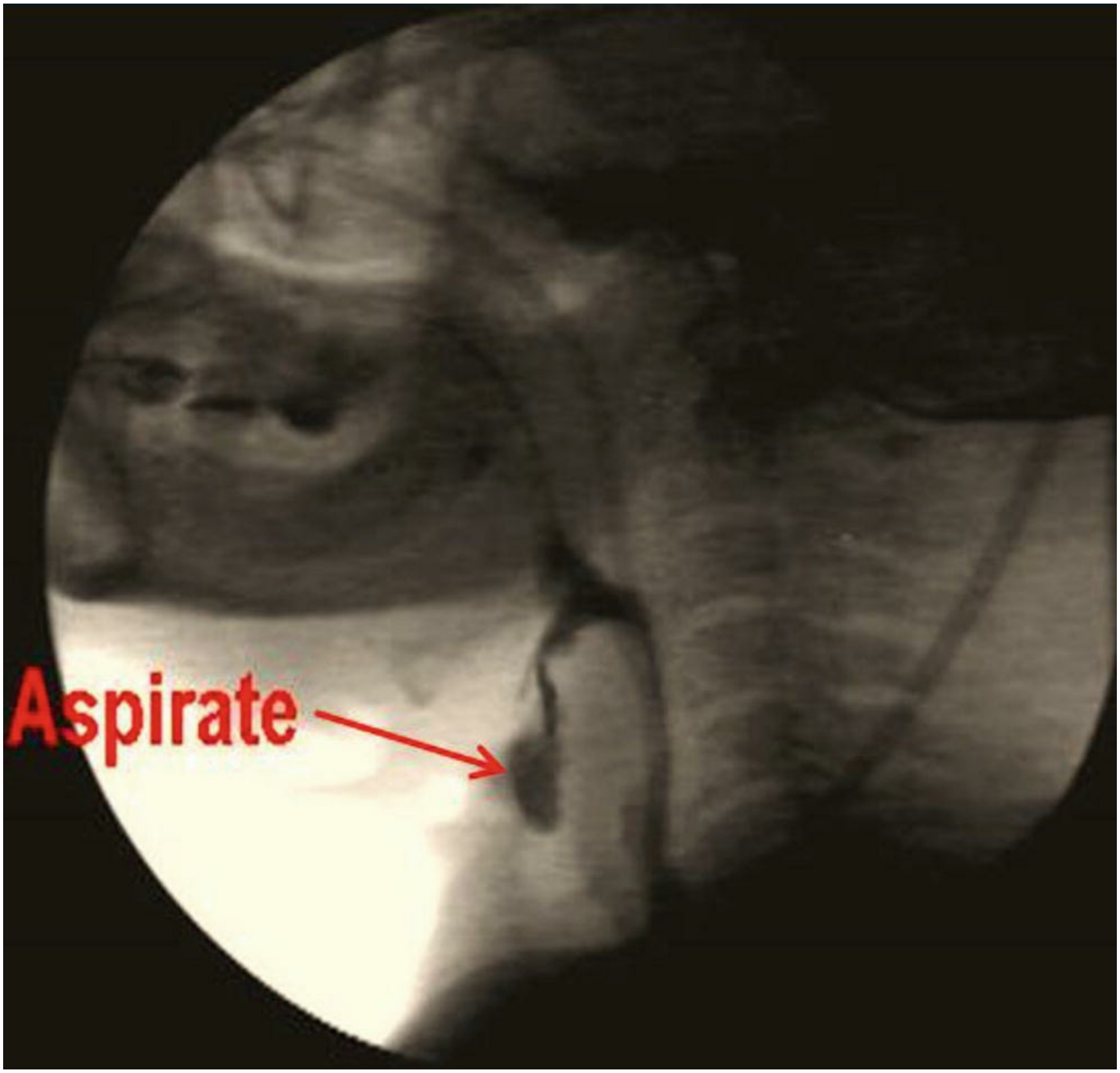

Figure 33.3. Aspiration is shown on MBS examination.

Flexible Endoscopic Evaluation of Swallowing

In some cases, FEES provides an excellent alternative to the MBS study because it can be easily performed as a clinical procedure or at bedside for patients who cannot tolerate or are not candidates for videofluoroscopic examination of swallowing. FEES uses a flexible endoscope placed transnasally to examine the pharyngeal swallow while providing direct visualization of laryngeal anatomy. FEES has been shown equally effective to the MBS study in detecting aspiration and does not expose the patient to

radiation.[44] It is often preferred for patients who have cancer of the larynx because it provides the best view of glottic competency, including airway protection and vocal fold mobility. An additional advantage of FEES is that it can be paired with simple sensory testing to help determine laryngeal sensitivity unlike the MBS study in which this is difficult to do.[45] Furthermore, it provides the patient with immediate biofeedback and visualization that are often useful during therapy sessions.

Unfortunately, the disadvantages of FEES often preclude its use for swallowing assessment in patients with cancers of the head and neck, particularly those that involve the oral cavity and the oropharynx. Neither the oral preparatory nor the oral phases of the swallow can be visualized during FEES. Thus, dysfunction must be inferred or presumed because of the "white-out" that occurs at the onset of the pharyngeal stage of swallowing that obscures visualization during the peak of deglutition. **Figure** 33.4 illustrates the laryngopharyngeal anatomy observed during FEES. Significant swallowing dysfunction is seen in **Figure** 33.5 during an FEES examination.

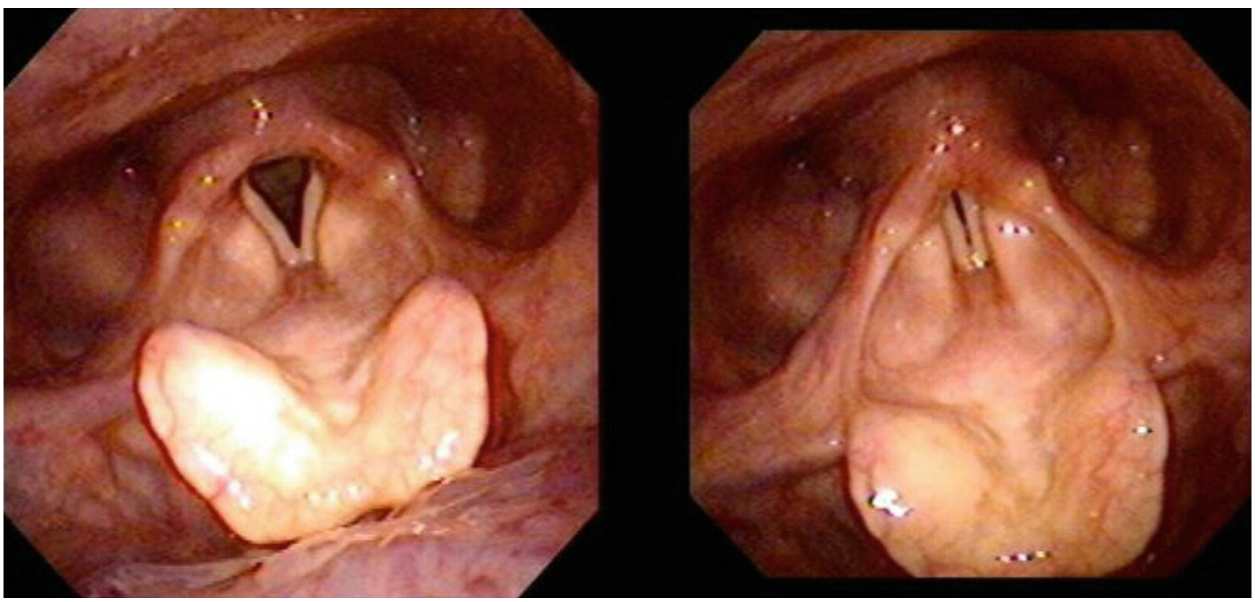

Figure 33.4. Fiberoptic view of laryngopharyngeal anatomy seen using FEES.

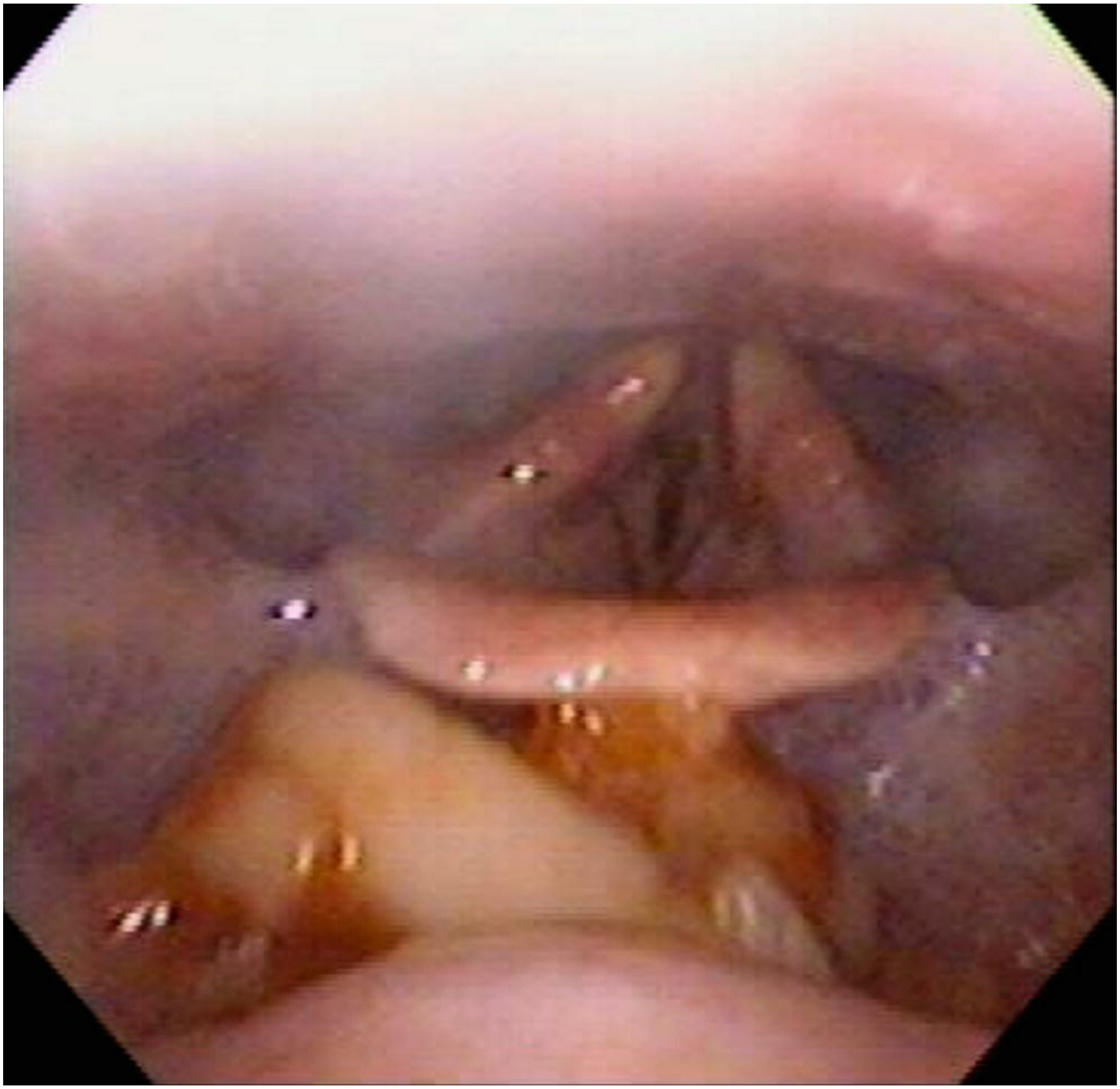

Figure 33.5. Abnormal FEES examination showing remaining significant amount of food in vallecular region after the swallow.

Laryngeal Videostroboscopy

Traditionally, evaluation of glottic functioning has relied on mirror examination of the larynx. Laryngeal videostroboscopy builds on the technique of mirror examination to visualize the glottis but also allows detailed examination of true vocal fold vibration to assess voice production. Laryngeal videostroboscopy should be coupled with acoustic and aerodynamic measures to accurately capture and document dysphonia. Most

critical is that laryngeal videostroboscopy remains one of the most useful tools to examine patients with cancer of the head and neck and vocal abnormalities because it exploits the limitations of observation with the unaided eye.

Videostroboscopic assessment employs the use of an endoscope that is placed transorally or transnasally and emits a straight and pulsed light to assess vocal fold movement and vibration. Videostroboscopy is generally performed as an office procedure. It affords a clinical measurement of movement that provides an illusion of slow motion and is a key diagnostic tool to visually assess pathology and function. Videostroboscopic imaging is not simply a photo, but rather it provides documentation of known disease and visualization of overall laryngeal anatomy and glottic functioning. It allows serial documentation and monitoring of change related to the treatment of laryngeal cancers. Because of the ability to evaluate vibratory function layer by layer, the trained examiner has an improved ability to determine the depth of vocal fold, superficial versus deep, that is prognostically important for decisions regarding surgical or nonsurgical treatment selection particularly for glottic cancers. In some instances, an early change seen on videostroboscopic examination may provide early indication of a cancer that would otherwise be invisible to the naked eye using indirect endoscopic visualization.

Finally, the use of videostroboscopy in the head and neck clinic often complements the images seen on CT scans because of the limitation in detection of subtle disease seen in the true vocal folds. The addition of laryngeal videostroboscopy frequently offers a greater capability for improved diagnostic accuracy of vocal fold disease. **Figure** 33.6 shows the image shown using a straight light during indirect visualization compared with **Figure** 33.7 that shows the vibration resulting from generation of a mucosal wave that can be seen using videostroboscopy.

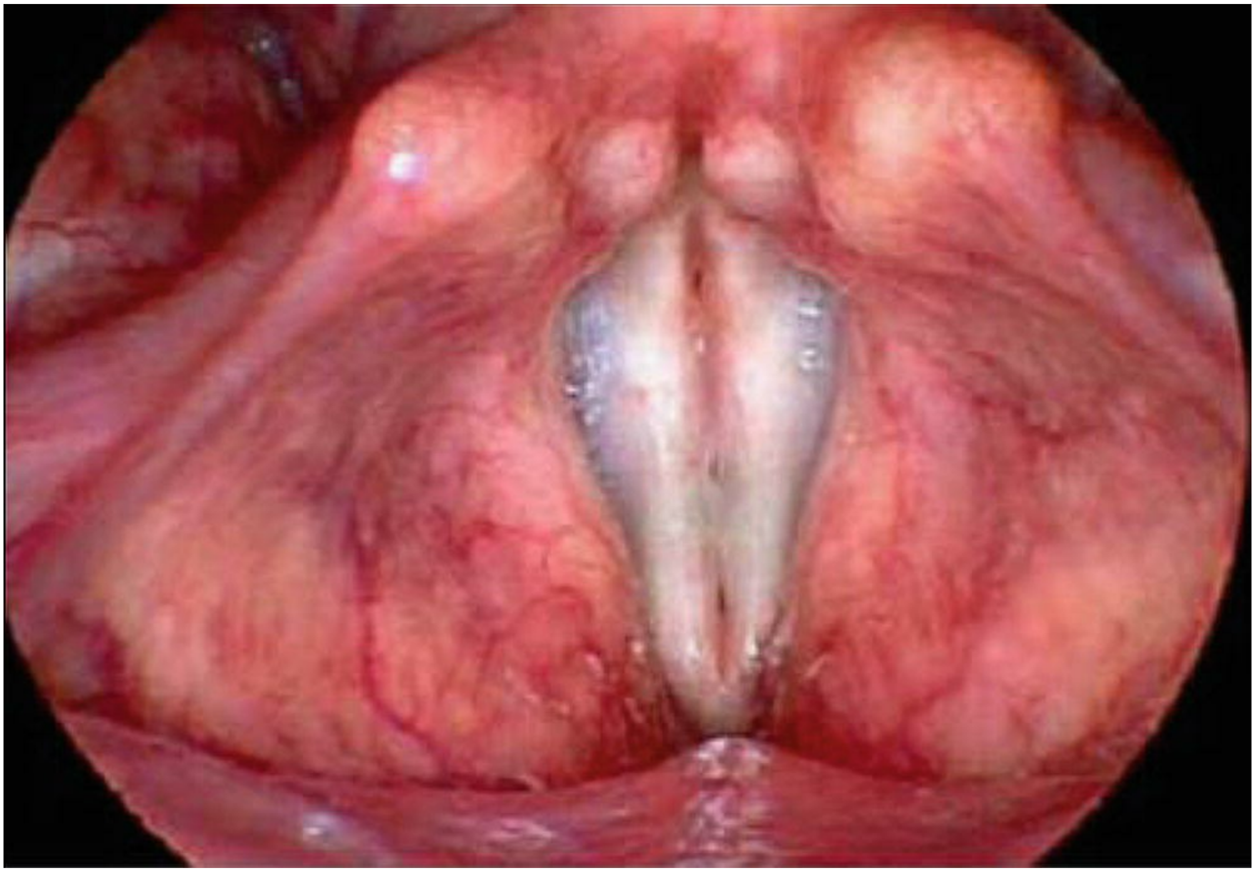

Figure 33.6. Straight light image of phonation.

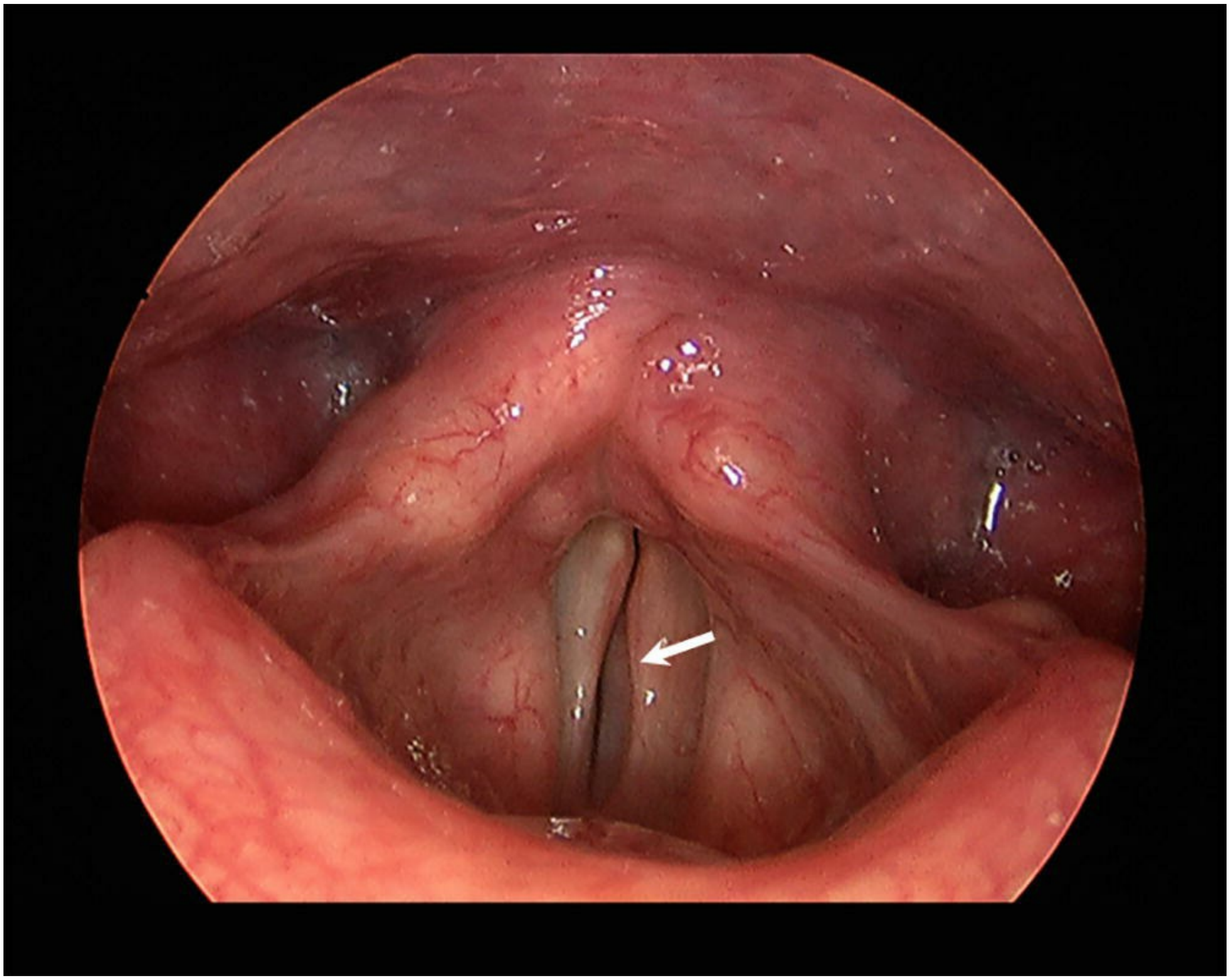

Figure 33.7. Videostroboscopic image of phonation. Note evidence of mucosal wave (*arrow*) along superior mucosal surface of left true vocal fold.

FUNCTION AFTER SURGERY

Postoperative speech and swallowing function basically depend on the primary site of tumor, the surgical approach, the type of reconstruction, and the extent of neck dissection. The addition of radiotherapy or chemoradiation as an adjuvant treatment after definitive resection of cancers of the oral cavity can exacerbate postsurgical effects because of the associated postradiation fibrosis and neuromuscular insult that will, in turn, impact laryngopharyngeal function.

In most cases, the extent of the cancer resection and the resulting surgical defect will determine the need for and the type of reconstruction. However, in general, larger defects that are reconstructed with adynamic, bulky flaps that

overfill the surgical defect will result in worse speech and swallowing outcomes. Primary closure generally is associated with the best postoperative function in selected reconstructions of the oropharynx.[46,47] Because of the increased use of nonsurgical organ preservation procedures in contemporary practice to improve locoregional control and preserve function for many patients with advanced cancer of the head and neck, the use of ablative surgeries has dramatically declined. Therefore, the popularity of traditional open surgeries such as the supraglottic laryngectomy and vertical partial laryngectomy that were often associated with increased complications and longer, more difficult rehabilitation and recovery has waned. Thus, open surgeries are primarily reserved for use as salvage procedures in cases of residual or recurrent cancers of the larynx and pharynx. As demographics change with an increasing percentage of head and neck cases being HPV-related oropharyngeal cancers, patients are now younger and healthier with a better prognosis for long-term survival. Hence, minimally invasive procedures that offer oncologic equivalency but result in quick recovery and rapid return to normal routine have become an expectation and a preference of today's patient with cancer of the head and neck.

Oral Cavity

Surgical resection remains the primary treatment modality used for cancers of the oral cavity.[48,49] In cases of cancer of the oral cavity, resection of critical structures of the oral cavity disrupts oral physiology and will result in problems with the oral stage of swallowing such as mastication and lingual propulsion. In addition, surgery that significantly impacts lingual structure and excursion are also associated with poorer swallowing outcomes. Surgical defects of the oral cavity are challenging to reconstruct because they require enough tissue to separate the oral cavity from the neck, prevent pooling, preserve remaining mobility, and restore anatomical configuration, but at the same time, they must avoid overcorrection with tissue bulk that obstructs oral swallowing function. Data have shown that the best swallowing outcomes result from partial resections that remove less than half of the tongue that are closed primarily.[50] Despite the ability to restore some sensation using new surgical techniques with innervated cutaneous free flaps, the ability to restore movement and function continues to be challenging, and no consensus has been reached regarding the functional benefit to both speech and swallowing

in patients who have undergone reconstruction with sensate flaps.[51]

Cancers of the oral cavity particularly those that involve the tongue most commonly impair articulation. However, in most cases, speech remains largely intelligible [sentence level (blinded rating): 92% to 98% intelligible] for surgically treated patients with advanced-stage cancer of the oral cavity (T stage ≥2) including cancers involving the tongue, but articulatory errors are common. Again, most patients will ultimately acquire good intelligibility after partial or hemiglossectomy that preserve half or more of the native tongue, but outcomes are more variable after subtotal and total glossectomy.[52] Besides articulatory defects, treatment of cancers of the oral cavity often affects oral speech resonance. Resection of cancer of the maxilla generally results in some degree of hypernasality until successful prosthetic obturation or surgical reconstruction of the defect is achieved.[53,54]

Swallowing efficiency (prolonged bolus transit times and incomplete bolus clearance) is commonly impaired after surgical management of advanced-stage cancers of the oral cavity, but chronic aspiration is less common (12% to 25% prevalence). Moreover, most patients with cancer of the oral cavity malignancies report the greatest degree of difficulty swallowing dry or hard foods.[55]

Oropharynx

Cancers of the oropharynx arise in a region of the UADT critical to swallowing function, and thus, pharyngeal dysphagia is the primary functional deficit after treatment. Minimally invasive surgery, specifically transoral robotic surgery (TORS), is fast becoming a preferred alternative over open surgical procedures or definitive chemoradiation for the treatment of oropharyngeal tumors. Likely, the primary advantage of TORS is the ability to preserve the suprahyoid muscles, which are critical for swallowing. Tracheostomy, typically required for airway management after open resection, is also avoided in most TORS cases (70% to 100%). Furthermore, lower rates of PEG tube placement (18% to 23%) and chronic PEG dependence (0% to 7%) after TORS are lower than those reported in patients receiving definitive chemoradiation. Finally, data suggest that 9% to 27% of patients treated initially with TORS avoid postoperative radiotherapy, and 34% to 45% avoid chemoradiotherapy.[17,56–59]

Larynx and Hypopharynx

The larynx plays a key role in both speech and swallowing function. It is the primary source of phonation for speech production. Its ability to move both superiorly and anteriorly is key to preventing saliva and food from entering the airway, thereby directing it into the cervical esophagus and on to the stomach. Thus, two of the most significant problems that affect swallowing following laryngeal surgery are the inability of the larynx to vertically and anteriorly elevate and to close. In addition to airway protection, these movements are essential to open the upper esophageal sphincter (cricopharyngeus) so that spillage into the trachea is avoided and food is directed into the esophagus. Hence, any surgery that impedes or limits laryngeal excursion or any of its valving mechanisms will result in swallowing dysfunction.

Most patients with early-staged cancer do not complain of significant swallowing problems postoperatively. Rather vocal dysfunction (dysphonia) is the primary complaint in the majority of patients who are treated surgically for early glottic cancer.[60–62] The increasing popularity of the use of transoral laser microsurgery (TLMS) instead of radiation therapy for early glottic cancers has provided significant benefit to carefully selected patients in terms of both vocal outcomes and reduced patient burden (missed work, reduced travel time to appointments, number of treatment sessions). Pretreatment videostroboscopic assessment provides valuable information regarding treatment selection, surgery versus radiation therapy, for patients with otherwise comparable survival outcomes for whom function becomes the determining criteria. Experience has shown that the depth of invasion and the glottic site of the cancer are key determinates in treatment selection. Cancers that deeply invade the vocal cord or ones that involve the anterior commissure are often better treated with nonsurgical alternatives that avoid large defects and impede vocal fold closure, resulting in glottic incompetency, poor vocal quality, and risk of aspiration. Unfortunately, there are few to no alternatives to augment or correct large, fibrotic defects of the glottis thereby resulting in poor quality of life for patients who are cured of their disease and for whom the prognosis for long-term survival is good.

Alternatively, surgical treatment for advanced cancer of the larynx is generally associated with problems of both voice and swallowing. Contemporary treatment for advanced cancer of the larynx includes larynx-

preserving resections that are often accompanied by adjuvant regimens of radiation therapy alone or in combination with chemotherapy. Although more ablative open surgery such as total laryngectomy and pharyngolaryngectomy are less frequently performed, they remain viable alternatives for the treatment of advanced cancer of the larynx that is not treatable with conservation alternatives and as salvage procedures for patients with persistent or recurrent laryngeal cancer.

Total Laryngectomy

Despite the contemporary goal of organ preservation, for some patients, this is not possible, and total laryngectomy remains the procedure of choice to enable cancer cure and survival. Despite the profoundly ablative nature of the surgery, total laryngectomy continues to be regarded as a quick, safe procedure with a high percentage of an ultimate cure of the disease. The surgical creation of a tracheal stoma and the loss of laryngeal voice represent the two major disadvantages of total laryngectomy. Despite these drawbacks, most patients who have had a laryngectomy report ultimate satisfaction particularly following successful tracheoesophageal (TE) voice restoration that is associated with recovery of a nearly normal ability to verbally communicate.[63–65]

Because total laryngectomy separates the trachea from the esophagus, the risk of aspiration is also avoided unless patients have also undergone tracheoesophageal puncture (TEP) for alaryngeal voice restoration. The ability to speak through a TEP depends on the surgical creation of an anatomical passageway between the esophagus and the trachea for the transfer of pulmonary air for sound production and hence reestablishes a potential site for tracheal aspiration of saliva and food. Recent data show that enlargement of the TEP may occur in up to 20% of patients. TEP enlargement can result in food and salivary aspiration around the TE voice prosthesis and can be associated with such etiologies as cancer recurrence, fibrosis, malnourishment, uncontrolled diabetes, and smoking. A retrospective multivariate analysis found that a history of advanced metastases to the neck, postoperative stricture, and locoregional recurrence/distant metastasis were the most significant risk factors for enlargement of the TEP in patients with a laryngectomy who were irradiated. Patients with advanced metastases to the neck who require extended neck

dissections are also at risk for TEP enlargement.[66]

Patients who have undergone total laryngectomy do not routinely complain of significant swallowing problems and in most cases return to a normal diet postoperatively. The majority of patients who have had a laryngectomy with dysphagia report slower swallowing that is primarily the result of pharyngeal dysmotility, cricopharyngeal dysfunction, and reduced strength of movements of the base of the tongue following resection of the larynx and hyoid bone. Patients frequently report an initial reduction in their sense of taste immediately after surgery. However, they generally indicate improvement in taste with healing.[67,68]

RADIATION THERAPY

Regardless of the clinical intent of radiation therapy as a definitive treatment modality, whether given in combination with chemotherapy for organ-preserving alternatives, as an adjuvant therapy following surgery, or for palliation of patients with incurable cancer, radiation produces tissue changes that, in many cases, result in long-term alterations in speech and swallowing function. In general, radiation has a greater effect on swallowing than it does on speech. Patients who have swallowing problems before treatment are at higher risk for chronic swallowing disability after treatment, and they are at higher risk for permanent feeding tube dependence.[69,70] The addition of chemotherapy and accelerated schedules of radiation can exacerbate the problems, particularly during the early phases of recovery. The magnitude of the effect will generally be influenced by the field or distribution of dose over the structures of the UADT, the radiation dose as it relates to the sensitivity of the structure to damage, the duration of treatment, and the fraction of treatments as the dose per treatment is associated with greater damage to function, particularly swallowing.

As the treatments for cancer of the head and neck have intensified in an attempt to improve both cancer cure and survival while still preserving the organ, so too have the treatment-related morbidities such as dysphagia, stricture, and pneumonia. Anecdotally, a late onset of radiation-associated dysphagia is relatively uncommon. However, a high prevalence (38.5%) is reported for dysphagia persisting more than 1 year after the completion of radiation therapy defined by chronic gastrostomy dependence, aspiration on

MBS, aspiration pneumonia, and/or stricture.[9,71]

When late radiation dysphagia occurs, the level of dysfunction is most often intense and debilitating. Recent data have shown that late, severe dysphagia is refractory to standard, nonsurgical therapies relegating patients' gastrostomy dependent and at high risk for aspiration pneumonia. Eighty-six percent of 29 long-term (≥5 years) cancer of the head and neck survivors with late dysphagia treated with radiation or chemoradiation therapy aspirated and developed pneumonia in a small case series study from a single institution. Sixty-two percent experienced recurrent pneumonias, and 21% ultimately underwent elective total laryngectomy to eliminate aspiration. Despite short-term benefit from standard rehabilitative efforts, no patient achieved durable improvement across all functional measures. Ultimately, 66% of these patients were gastrostomy dependent as a result of aspiration or malnutrition.[72]

Data have shown that early swallowing recovery from radiation therapy may be misleading because of the delayed development of fibrosis and cranial neuropathies that cause neuromuscular dysfunction and impede swallowing physiology resulting in long-term swallowing deterioration. Findings support the neuropathic contributions to posttreatment dysphagia as a result of the denervation of the suprahyoid musculature following radiation therapy.[73] Late-swallowing dysfunction and aspiration have been reported in up to 60% of patients treated with radiation therapy, and up to 70% of patients who aspirate do so silently without coughing or clearing their throat. It has been estimated that between 15% and 30% of patients who aspirate will require a feeding tube for nutrition. Persistent dysfunction has been reported after treatment, months or even years later.[74–76] Although stricture has mostly been seen in areas that receive high-dose radiation, stricture has also occurred in areas treated with lesser radiation doses. Thus, authors have suggested that decreased swallowing frequency may also be associated with increased risk of fibrosis.[77] Rather than stricture, it is therefore more likely that the commonly reported problems associated with dysphagia including reduced pharyngeal contraction, limited base of tongue retraction, incomplete epiglottic inversion, decreased laryngeal excursion, and abnormal esophageal opening are more likely the primary contributors to late, severe radiation-associated dysphagia.[72] A rate of 16.7% pharyngoesophageal stricture was reported in patients treated with IMRT using photon beam therapy compared

with 5.7% in patients treated with conventional radiation therapy, again suggesting an effect of treatment intensification despite normal tissue sparing and protection.[78] Recent findings have shown increased beam path toxicity from higher doses of IMRT delivered to nontargeted structures including the brainstem and oral cavity, compared with that associated with the administration of 2D conventional radiation.[79] In all cases, the avoidance of specific organs at risk is important to swallowing preservation.[80–82] Newer treatment techniques including IMRT and IMPT (protons) that target the cancer with set radiation doses while limiting the dose to adjacent structures may reduce radiation-related morbidity. Thus, dose-limiting constraints to organs at risk may avoid long-term swallowing dysfunction.

COMMON COMPLICATIONS OF TREATMENT

Two of the most common complications resulting from radiation-induced damage to the salivary glands and mucosal tissue of the UADT are xerostomia and mucositis. Xerostomia is one of the most disturbing complaints of patients treated with radiation as there are no good, effective long-lasting management strategies to mitigate dry mouth. Acute mucositis is also associated with long-term dysphagia and has been reported to be a major dose-limiting toxicity of standard chemoradiation regimens. High-grade mucositis resulting from intensive regimens of chemotherapy generally occurs early, lasts longer, is more severe, and may result in scarring and organ dysfunction. Patients experience thick, ropey secretions that are difficult to swallow or expectorate and result in gagging, regurgitation, and, in some cases, aspiration.[83] Patients who receive oral irradiation and experience mucositis and xerostomia often present with reduced lingual speed, slow oral transit of food, aberrant tongue movements, and slowed triggering of the swallow reflex.[84] Other complications from radiation therapy that affect speech and swallowing function include trismus, dys- or ageusia (changes in or loss of taste), and dysosmia (changes in smell). These problems often begin acutely and worsen throughout treatment.

Head and neck lymphedema (HNL) is another common sequela of HNC treatment that is associated with symptom burden, functional deterioration,

and poor quality of life in HNC survivors.[85,86] Although interest in HNL has increased, unfortunately HNL continues to be an underrecognized and undertreated functionally debilitating consequence of treatment that has been estimated to occur in at least 50% of treated HNC patients.[87,88] HNL is characterized by tissue swelling resulting from the blockage of normal drainage pathways in the lymphatic system. Although most often associated with radiation effects that impair vessel contractility (“lymphangiomotoricity”), surgery that removes lymph nodes as well as the tumor itself may cause vessel obstruction. In some cases, infection such as recurrent cellulitis may further impair lymphatic functioning.[89,90] If left untreated, chronic edema along with permanent fibrosis can result in significant long-term cosmetic, functional, and psychosocial consequences that are often irreversible, including discomfort and difficulties associated with speech, respiration, voice, and swallowing.[91] **Figure** 33.8 represents typical presentations of patients with HNL after treatment of their head and neck cancer.


A

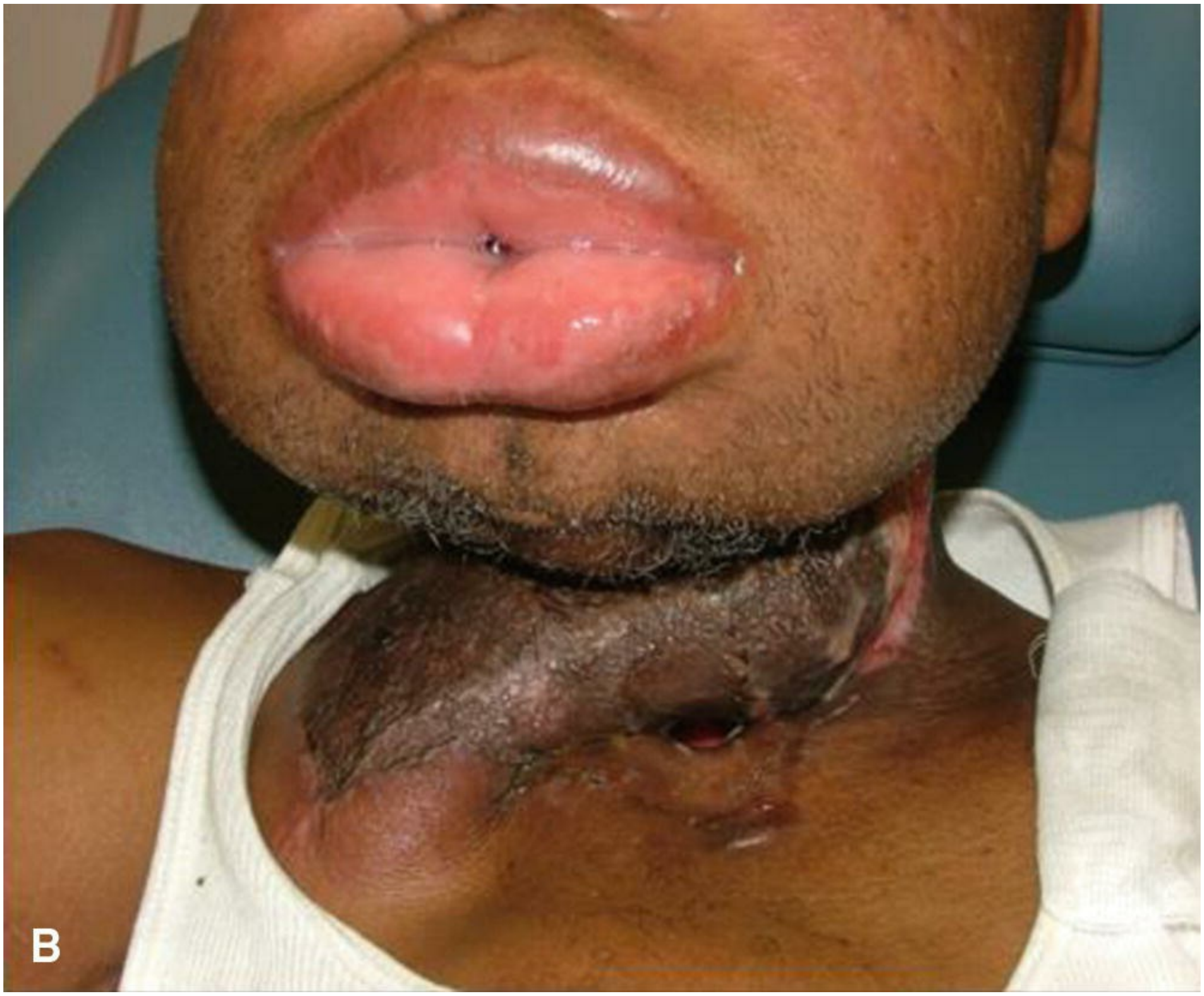
B

Figure 33.8. A–C: Typical presentations of HNL after treatment for cancer of the head and neck.

A recent analysis of over 1,200 survivors of cancer of the head and neck with HNL showed that 68% of patients with functional complaints reported swallowing problems. Swallowing dysfunction is readily illustrated in the radiographic views shown in **Figure** 33.9. Furthermore, 60% of patients showed dramatic reduction in HNL regardless of complete or partial adherence to complete decongestive therapy that was mostly self-administered by the patient through a home program after training by a certified HNL therapist.[92] Dramatic results after treatment for HNL can be seen in **Figure** 33.10.


A

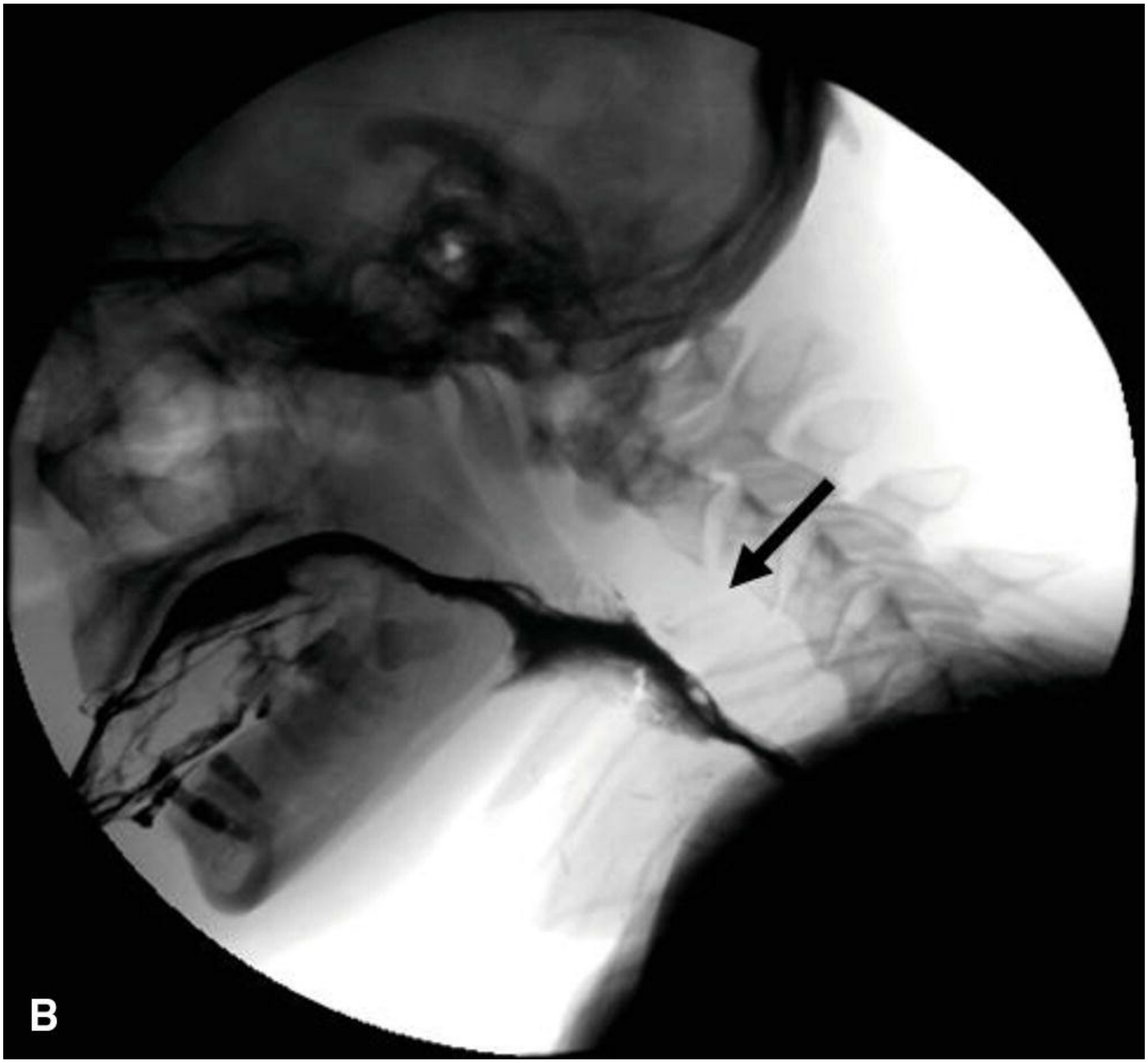

Figure 33.9. A: Loss of food from the mouth as a result of severe edema of the lip. **B:** Pharyngeal narrowing with food stasis as a result of prevertebral edema.


A

Figure 33.10. A: Marked HNL before complete decongestive therapy. **B:** Note the significant improvement after therapy.

PREVENTION AND TREATMENT

Prevention of Dysfunction

Intact oral, pharyngeal, and laryngeal anatomy and physiology are critical to speech and swallowing function. The lips, oral tongue, and soft palate play critical roles as the articulators of the oral cavity and are essential for speech production. Speech intelligibility depends on a highly precise sequence of rapidly changing vocal tract shapes resulting from exquisitely precise movements and articulatory contacts. The valving action of the velum determines the nasality of sounds. Laryngeal valving requires the opening or closing of the vocal folds to produce the voiced distinction between sound pairs. Consequently, speech intelligibility can be significantly impaired by partial, subtotal, or total glossectomy but can be improved with speech therapy even after major or total resection.[93,94]

Likewise, the same structures are also essential to the efficiency and safety of normal swallowing including the lips to contain the food, tongue to propel it through the oral cavity into the pharynx, palate to prevent nasal regurgitation, and larynx to avert aspiration. Cephalad laryngeal excursion leading to epiglottic closure and adduction of the vocal folds is a critical component of glottic airway protection. The primary correlates of swallowing dysfunction include poor retraction of the base of the tongue, pharyngeal dysmotility, poor laryngeal excursion, and impaired airway closure (glottic or neoglottic). Thus, treatment of cancer of the head and neck that avoids or reduces damage to these structures will, in effect, help prevent long-term problems as any insult to these structures or their physiology can impair both speech and swallowing function.

Conformal plans using IMRT have been proposed to prevent the burden of dysphagia by limiting radiation dose to the base of the tongue, pharyngeal constrictor muscles and autonomic neural plexus, and the larynx, essentially sparing swallowing-related organs at risk.[81] The unnecessary radiation of the uninvolved larynx has been strongly discouraged in contemporary radiation treatment planning.[95,96] There are different techniques used during IMRT. Some treat the entire neck with IMRT, or split the field, and treat the lower neck with an anterior supraclavicular field that essentially blocks or limits larynx dose and is associated with lower aspiration rates, a potential benefit over other radiation techniques for the prevention of swallowing dysfunction.[80]

Research findings show that delaying the placement of a feeding tube until it is needed may in fact help preserve long-term swallowing function. The practice of prophylactic feeding tube placement for patients with cancer of the head and neck has changed within the last decade as evidence has shown that patients who receive prophylactic G-tubes are more likely to have late esophageal toxicity and dysphagia, leading to long-term dependence on enteral feedings and often depression that ultimately complicates recovery.[19,97,98] Recent findings suggest that reactive versus prophylactic feeding tubes are associated with favorable swallowing outcomes and thus may help to prevent dysphagia requiring long-term feeding tube dependence. Furthermore, experience has shown that reactive feeding tube placement is in fact possible without increasing the rate of breaks in cancer treatment. In a study of 474 evaluable patients with oropharyngeal cancer of whom 293 patients (62%) required placement of a g-tube during the study period; no patient required a treatment break for g-tube placement.[24]

Data clearly demonstrate that early therapeutic regimens of swallowing exercises that are designed to strengthen musculature, increase the precision of movements, and maintain range of motion provide the best prevention of long-term swallowing dysfunction in patients who have undergone radiation or chemoradiation therapy for cancer of the head and neck.[99,100] Because even brief NPO intervals (≥2 weeks) portend poorer swallowing outcomes, experience shows that it is important for patients to continue to swallow as frequently and as much as possible throughout the course of their radiation treatment, even if they have a feeding tube, to maintain swallowing ability.[19,20]

Moreover, prophylactic swallowing exercise that begins before the initiation of cancer treatment is associated with better swallowing–related quality-of-life scores,[101] superior movement of the base of tongue and epiglottis,[102] lower gastrostomy rates,[24,103] better postradiation therapy diet levels,[104] improved mouth opening,[105] and superior muscle composition on MRI.[106] Results demonstrate that both eating and exercising are associated with the best swallowing outcomes; however, eating or exercising alone results in better outcomes than does neither eating nor exercising. Moreover, findings also show that patients who adhere to their swallowing exercise regimens are 3.6 times more likely to eat a regular diet in long-term survivorship than do those who do not adhere.[107]

Treatment and Rehabilitation

Impaired voice production associated primarily with the treatment for cancer of the larynx, including both surgical and nonsurgical management, can range from breathiness or hoarseness to complete aphonia. Depending on the etiology, speech therapy alone or in combination with any one of a variety of surgical procedures designed to improve and optimize voice production may be recommended, particularly in cases of unilateral vocal fold paralysis. In appropriately selected cases, injection medialization laryngoplasty (thyroplasty) offers temporary augmentation for relief of acute aspiration related to glottic incompetence. For patients whose paralysis is long standing, permanent medialization thyroplasty offers the opportunity for return of near-normal vocal function and efficient glottic airway protection.[108,109]

Probably the most significant voice disorder requiring specialized expertise is the rehabilitation of voice after total laryngectomy. Total laryngectomy results in a variety of cosmetic and functional changes; however, the most debilitating is the loss of verbal speech production. Verbal communication is restored using three major approaches: (1) the artificial larynx or electrolarynx, (2) esophageal speech production, and (3) surgical prosthetic voice restoration, of which the most common and contemporary method is TE voice restoration with a removable voice prosthesis. Not every patient is a candidate for all of the alaryngeal speech alternatives, and selection should be made on the basis of careful evaluation. The advantages of each alaryngeal speech alternative should be reviewed and discussed with the patient prior to surgery. Recommendations should be based on the individual's specific needs and interest, medical/surgical history, physical capabilities, level of independent functioning, family support, motivation, and access to and compliance with rehabilitation. In the case of TE voice restoration, the ability to acquire replacement prostheses is a consideration that is frequently neglected. Access to well-trained, expert clinicians who can help manage issues related to placement of the TE prosthesis or who can problem-solve difficulties encountered by the TE speaker is often challenging. In addition, the cost of prostheses may be prohibitive for patients who have limited funds and for whom TE prostheses are not a covered benefit of their insurance policies.

The choice of an alaryngeal method is primarily a function of the patient's ability to choose based on his or her physical and medical status and

personal preference, and the decision regarding the best alaryngeal speech alternative should never be made solely by the physician, speech pathologist, or family. In large part, clinician experience and familiarity with the specific alaryngeal voice alternative will significantly impact the patient's overall success in acquiring alaryngeal speech production. Thus, it is important that alaryngeal speakers seek out rehabilitation from experienced clinicians who are familiar with the nuances of multiple available methods and who are not unfamiliar with the unique complications and problems often experienced by alaryngeal speakers.

CONCLUSIONS

Cancer of the head and neck and its treatment result in unique problems that require clinician expertise and familiarity with the disease, the treatment and its effects, and the rehabilitation and restoration of associated speech and swallowing dysfunction. Contemporary focus on quality of life and functional preservation, surgical and nonsurgical, will likely play a key role in future decisions regarding treatment for cancer of the head and neck as today's survivor is typically younger, healthier, and better informed, with a greater chance for increased survival, and an expectation for functional success along with a quick return to a normal premorbid routine. Late treatment effects associated with intensive treatment regimens, especially those associated with radiation, are not generally common, but when they occur, they can be devastating. Thus, current intervention to protect the ability to speak and swallow must be targeted and aggressive based on the findings of functional examinations that start early and are rigorously monitored to ensure progress and avoid complications. It is critical that ongoing and future investigations into treatments for cancer of the head and neck ensure cure and survival, but avoid crippling speech and swallowing function in our survivors.

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34 Supportive and Palliative Care

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INTRODUCTION

Palliative care is a discipline that strives to alleviate the physical and psychological suffering of patients and their families and to allow them to express their maximum potential during the course of their illness.

Patients with cancer of the head and neck may suffer from severe symptoms, including pain, anorexia, fatigue, cachexia, dyspnea, and psychological distress. In addition, cancer treatments such as surgery, radiation, chemotherapy, and immunotherapy have adverse effects such as mucositis, neutropenia, infection, neurocognitive dysfunction, and psychological distress due to extensive surgical procedures. The purpose of this chapter is to discuss the assessment and management of these complex symptoms in patients with cancer of the head and neck at all stages of their disease.

SIGNS AND SYMPTOMS ASSOCIATED WITH CANCER OF THE HEAD AND NECK

Cancer of the head and neck is frequently associated with many physical symptoms related to the cancer itself or to associated treatment. Surgery and radiation therapy are the main modes of treatment, although chemotherapy is frequently used.[1] Radiation therapy doses sufficient to produce tumor regression are associated with mucositis and xerostomia (dry mouth).[2] In addition, significant disfigurement and functional loss often accompany surgical interventions.[3] Many vital functions such as taste, speech, mastication, and swallowing can be affected.[4] Late effects of treatment,

particularly radiation ports that include incidental brain exposure, may cause significant cognitive impairment.[5] Cancers of the head and neck are particularly problematic because of their impact on the airway and gastrointestinal tract, which results in significant compromise of breathing and nutrition. **Table** 34.1 describes the incidence of the most common symptoms of advanced cancer of the head and neck.

Table 34.1 Incidence of Common Signs and Symptoms of Advanced Cancer of the Head and Neck

Symptom	Approximate Percentage
Pain	79
Weight loss	79
Feeding difficulties	74
Dysphagia	74
Cough	66
Communication	53
Bleeding	47
Candida	47
Fistula	21
Aspiration	10

Modified from Forbes K. Palliative care in patients with cancer of the head and neck. *Clin Otolaryngol.* 1997;22:117.

Pain

Pain is a common symptom in this patient population. In most patients with advanced cancer, chronic pain is due to direct stimulation of afferent nerve structures by the primary or metastatic cancer. Pain associated with direct tumor involvement occurs in 65% to 85% of patients with advanced cancer.[6] Cancer therapy accounts for 15% to 25% of pain syndromes.[7] Pain

syndromes are categorized as nociceptive or neuropathic. Nociceptive pain is further divided into somatic and visceral. For example, nociceptive pain related to cancer of the larynx or bony metastases results from activation of pain receptors in these tissues and organs. Neuropathic pain, such as trigeminal or glossopharyngeal neuralgia, results from direct injury to the peripheral or central nervous system. Somatic pain is usually localized and tender to pressure; neuropathic pain is often described as burning or shooting.[8]

Patients with advanced cancer often have chronic, constant pain intermittently punctuated by acute breakthrough pain. Patients may have acute pain following certain procedures, such as postoperative pain or radiation-induced mucositis. Incidental pain is usually acute and may be triggered by certain maneuvers such as swallowing, mastication, or speech.

Weight Loss

Cachexia–anorexia occurs in more than 80% of patients with advanced cancer and is a major factor contributing to morbidity and mortality.[9] Patients with cancer of the head and neck are particularly susceptible because of the effects of cancer and its treatment on eating, including altered taste and difficulty chewing and swallowing. Cachexia is characterized by weight loss, wasting, anorexia, and change in body image with resulting asthenia and psychological distress.

Fatigue

Fatigue is the most frequent symptom of advanced cancer.[10] It is characterized by unusual and profound tiredness after minimal effort, accompanied by an unpleasant sensation of generalized weakness. Cancer-related fatigue, unlike fatigue in a person who is not ill, does not improve with rest.

Psychological Distress

Patients with cancer of the head and neck face enormous psychological distress because of the structural and functional deficits associated with the cancer and its treatment. Facial disfigurement and loss of taste, speech, and sometimes sight result in altered body image, low self-esteem, and possibly

depression.[11] Moreover, patients with cancer of the head and neck often have a history of chronic alcohol and tobacco use[12] accompanied by physical and neurocognitive disabilities.[13] It is estimated that 80% of patients with cancer of the head and neck have such a history, which may complicate their care and rehabilitation.[14]

ASSESSMENT OF SIGNS AND SYMPTOMS

Pain

Lack of expertise among health care professionals in the use of assessment tools for pain and other symptoms is the main reason for poor management of symptoms.[15] Patient self-reporting should be the primary source of information for the measurement of symptoms. Observer ratings of symptom severity correlate poorly with patient ratings. Simple tools such as the visual analogue scale (VAS), numeric rating systems (NRSs), and verbal descriptor scales have proved to be effective and reproducible means of measuring pain and other symptoms.[16] Other scales include the Memorial Symptom Assessment Scale (MSAS).[17] The Edmonton Symptom Assessment System (ESAS) is the most common clinical tool for the assessment of pain and multiple other physical and psychosocial symptoms in the clinical setting (**Fig.** 34.1). This tool is copyright-free and can be completed by the patient in a few minutes. Pain in cancer patients is frequently complicated by a high level of distress.[18] The emotional suffering experienced by cancer patients manifests itself as fear, anxiety, and depression, which result in increased sensitivity to pain and other symptoms.[19] Therefore, a unidimensional approach to pain that considers 100% of the pain complaint as nociceptive may not address other treatable conditions, thus depriving the patient of appropriate additional therapies.

Referral Date:					Referring Physician:							
Date:												
Pain (0–10)*												
Fatigue (0–10)*												
Nausea (0–10)*												
Depression (0–10)*												
Anxiety (0–10)*												
Drowsiness (0–10)*												
Shortness of breath (0–10)*												
Appetite (0–10)*												
Sleep (0–10)*												
Feeling of well-being (0–10)*												
Mini Mental State Score (0–30)												
Assessment from: Pt/SO/HCP (If SO or HCP—use red ink)												
Total opioid MEDD: mg/day												
Staff initials (signature and title below)												

* 0 = No symptoms/ Best 10 = Worst Imaginable

Figure 34.1. Edmonton Symptom Assessment System. (From Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System [ESAS]: A simple method for the assessment of palliative care patients. *J Palliat Care*. 1991;7:6–9.)

Assessment of pain should address the cause of the pain and should measure the intensity, onset, duration, location, character, and factors that aggravate and relieve it. Regular reporting in the patient's medical records of the patient's pain and other symptoms assists the team that is treating the patient in monitoring these symptoms and providing appropriate treatment. The ESAS (Fig. 34.1) graphically displays the most common symptoms reported among cancer patients.[20–22]

A positive history of alcoholism may be associated with a higher risk for the use of medications to cope with emotional distress.[23,24] Well-validated tools are available for quantifying alcohol use, both current and past,[25]

although there are limitations to the accuracy of any self-report questionnaire about alcohol use. Some groups have found that a history of alcoholism is an independent prognostic factor for the development of opioid dose escalation and opioid-related neurotoxicity[26] and that such a history predisposes the patient to preexisting cognitive deficits.[27] Simple bedside screening of alcohol intake shows a very high frequency of undocumented alcoholism. These patients are at a higher risk of chemical coping with opioids.[28] Among patients with head and neck cancer, those who score positive in the CASE questionnaire are at high risk of opioid use 3 months and 6 months after completion of radiation and/or chemotherapy. Although patients with a significant alcohol history may need more frequent monitoring and counseling to achieve good pain control, a history of substance abuse or emotional problems is not an indication for limiting pain treatment.

Unfortunately, pharmacologic treatment of pain may lead to worsening of other symptoms such as opioid-related nausea, constipation, and delirium. Given the complexity of the interaction among the various physical and psychosocial domains, there is a growing acceptance that the assessment of pain in cancer patients requires a multidimensional approach.

Weight Loss

Weight loss is the main clinical finding in patients with cancer cachexia. In patients with cancer of the head and neck, this may result from local factors affecting food intake such as altered taste, smell, or swallowing. It may also be due to decreased appetite. A weight loss of 10% or more usually indicates moderately severe malnutrition.[29] The presence of edema, ascites, or pleural effusion may make the interpretation of weight loss difficult. Assessment of caloric intake can be made at the bedside by a nutritionist or a trained nurse. Anorexia is a major target of both nutritional and pharmacologic interventions.

Fatigue

Fatigue is often measured according to subjective assessment and functional capacity. Commonly used performance status scales, such as the Karnofsky Performance Scale and the Eastern Cooperative Oncology Group (ECOG) scale, do not adequately measure fatigue. Although there are a number of

tools for the assessment of the severity of fatigue, in the clinical setting, it can be monitored using multidimensional tools such as ESAS.[30]

MANAGEMENT OF SIGNS AND SYMPTOMS

Pain

Successful management of pain depends on the physician's ability to assess the patient and the pain, identify the pain syndrome, and formulate and discuss the treatment plan with the patient. A pharmacologic approach is the primary treatment provided for cancer pain. In more advanced and complex cases, in which suffering and psychological distress complicate pain perception, a multidisciplinary approach is required for effective pain management. The World Health Organization proposed a simple analgesics ladder for the pharmacologic management of cancer pain, which has been shown to be safe and effective. This ladder begins with simple nonopioid analgesics, proceeds to weak opioids, and then recommends strong opioids as the disease progresses and pain expression escalates. Most patients need opioids for the management of cancer pain. Patients should receive appropriate counseling and information regarding their pain, opioids, medication adverse effects, and the costs of treatment.

Nonopioid Analgesics

Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) are effective analgesics for patients with mild cancer pain and can be combined with opioids such as codeine and oxycodone in patients with moderate to severe pain.[31] Acetaminophen does not inhibit prostaglandin synthesis or affect platelet function; therefore, it is widely used in the treatment of cancer pain, either alone or in combination with opioids such as codeine or oxycodone. The major toxicity of acetaminophen is its hepatotoxic effect, which is dose related. Therefore, the cumulative daily dose should not exceed 4 g. The main limitations of NSAIDs include their relatively flat dose–response curves and associated gastrointestinal, renal, and bleeding adverse effects. These effects are related to the inhibition of the enzyme

cyclooxygenase-1. Newer generations of cyclooxygenase-2 inhibitors such as celecoxib and rofecoxib have a lower frequency of toxicity and are effective when used alone or in combination with opioids.

Opioids

Opioids remain the mainstay in the treatment of cancer pain. Opioids interrupt pain perception at different levels in the central nervous system. **Table** 34.2 summarizes the general principles that apply to opioid treatment of cancer pain.

Table 34.2 Opioid Treatment of Cancer Pain
Administer around the clock.
Aggressively prevent nausea and constipation.
Consider adjuvant drugs to manage adverse effects or a specific pain syndrome.
Consider long-acting opioids when pain is better controlled.
Consider opioids as only one part of the total pain management plan.
Educate patient regarding tolerance, adverse effects, and low risk of addiction.
Make oral route the first choice.
Titrate doses individually. Allow extra doses for rescue analgesia.

Routes of Opioid Delivery.

The oral route of opioid administration is preferable because it is safe, effective, and convenient and can be used in the home setting. However, 80% of patients taking oral opioids require an alternative route of administration before death.[32] The intravenous route is more suitable for the immediate postoperative period and when the gastrointestinal route is not available

because of concerns about wound healing, vomiting, dysphagia, or mucositis. Patient-controlled analgesia (PCA), administered with different types of pumps, is a widely used technique that has proved to be effective in the treatment of pain in hospitalized patients, especially during the postoperative period.[33] Although the overuse of medication by confused or psychologically impaired patients, particularly those with a history of addiction, is possible, this is easily handled by limiting the number of doses that can be administered over a given period of time. The subcutaneous route is a safe and effective mode of opioid delivery wherein opioids can be administered by the patient or a family member with the use of a preloaded syringe.[34] The rectal route is also safe and effective, but it is uncomfortable for many patients. The transdermal route (patch) is an effective alternative to the oral route and is more suitable for patients with stable pain complaints who need a relatively small dose of opioids. Drugs such as morphine and hydromorphone can be given safely through the transdermal route.

Specific Opioids.

Patients with cancer-related pain need to be maintained on opioids in such a way that a constant blood level of the drug can be provided. In addition, patients need to have access to rescue doses of opioid for episodes of pain exacerbation. **Table** 34.3 summarizes the opioids most frequently recommended for cancer pain.

Table 34.3 Opioid Analgesics Most Frequently Recommended for Cancer Pain

Type of Opioid	Name of Opioid	Common Route	Equivalent Price ($)	Other Routes
Weak	Codeine[a]	PO	—	IV, SC
	Tramadol	PO	—	—
Strong	Morphine	PO	1	IV, SC, Supp
	SR Morphine	PO	5	—
	Hydromorphone	PO	3	IV, SC, Supp
	Oxycodone	PO	3.6	SC[b]
	SR Oxycodone	PO	6.5	—
	Fentanyl	TD	6.5	TM, IV
	Methadone	PO	0.15	IV, Supp
	Diamorphine[b]	IV	—	SC

[a]Products may contain paracetamol. Make sure the daily paracetamol dose does not exceed 4 g.

[b]Not available in the United States (available in Canada and the United Kingdom).

$, Approximate relative price when a daily dose equivalent to morphine 100 mg by mouth is used.

PO, oral; IV, intravenous; SC, subcutaneous; Supp, suppository; TD, transdermal; TM, transmucosal; SR, slow release.

Weak Opioids.

Members of this group, including codeine and tramadol, tend to have a flat dose–response curve and are frequently associated with fewer restrictions for prescriptions. Codeine is frequently combined with acetaminophen or aspirin. Propoxyphene is not recommended for long-term use in cancer pain because it includes the active metabolite norpropoxyphene, which can cause confusion and hallucinations. Recent research has demonstrated that hydrocodone is 1.5 times more potent than morphine and therefore it should not be considered a weak opoid.[35]

Strong opioids.

Morphine has been considered the strong opioid of choice. However, other opioid agonists such as hydromorphone and oxycodone exhibit similar properties. A typical starting dose of morphine is 5 to 10 mg every 4 hours in patients who have not taken opioids previously. The starting dose may not be sufficient, and relatively rapid titration may be needed, particularly if pain is severe. When the effective dose of short-acting morphine has been established, patients may be maintained on this preparation, or at this point, a slow-release preparation may be administered every 12 or 24 hours. When a patient is switched from one opioid to another, or when one opioid is substituted for another, it is important for the clinician to calculate the equianalgesic dose of the previous opioid to determine the correct dose of the new opioid.

Hydromorphone is a semisynthetic derivative of morphine that is approximately five to six times more potent. It is well absorbed from the gastrointestinal tract. Usually, it is given as an immediate-release preparation every 4 hours, although in some countries such as Canada, slow-release preparations are available.

Methadone is a synthetic opioid with good bioavailability; it is inexpensive and less constipating than other opioids, making it a suitable

drug for the treatment of chronic cancer pain. It has no active metabolites; therefore, it is particularly useful in patients with renal failure. However, methadone has a prolonged and unpredictable half-life and complex pharmacokinetics, making it relatively difficult to titrate. Currently, the practice of starting treatment with methadone should be limited to physicians who are experienced with its use.

Fentanyl is available as a transdermal patch with ~3 days duration of action. A disadvantage of fentanyl is the difficulty associated with titrating the dose when a steady state is not reached.

Meperidine should not be used on a long-term basis for cancer pain because of the associated production of a neurotoxic metabolite, normeperidine, which can cause seizures and other central nervous system adverse effects.

Adverse Effects Associated with Opioids.

A number of adverse effects are associated with the use of opioids for cancer-related pain. In most patients, these adverse effects can be managed easily through patient education, selection of the appropriate route of administration, and the use of additional drugs such as antiemetics and laxatives. **Table** 34.4 summarizes the main adverse effects of opioids.

Table 34.4 Common Adverse Effects of Opioids

Problem	Suggested Intervention
Cognitive slowing	Consider opioid rotation, improved hydration; review current psychoactive medications and educate family.
Constipation	Start laxative concomitantly (e.g., senna products). Titrate the dose.
Nausea	Start metoclopramide 10 mg every 4 h around the clock for 3 d, then as needed.
Pruritus	Give antihistamine.
Respiratory depression	Reduce the opioid dose for mild depression. If moderate or severe, treat with opioid antagonists (e.g., naloxone).
Sedation	May improve spontaneously with continued use. If it persists, consider psychostimulant (e.g., methylphenidate).

Sedation, constipation, and nausea are the most common adverse effects. Sedation and nausea usually improve spontaneously in about 3 days. Sedation can be exacerbated by coadministration of alcohol or benzodiazepines. If sedation persists, the administration of a psychostimulant such as methylphenidate may improve arousal during the day.[36] Nausea is caused by

the opioid effect on the chemoreceptor trigger zone and by delayed gastric emptying. Antiemetics such as metoclopramide are effective against both mechanisms.

Constipation is the most common adverse effect of opioids. Opioids act at multiple sites in the gastrointestinal tract to decrease both peristalsis and intestinal secretions. Unlike sedation and nausea, tolerance to constipation develops very slowly. Therefore, patients will most likely require regular laxative treatment for the duration of opioid therapy. A major myth is that constipation is a normal response to poor oral intake. Health care providers should be educated about the physiologic shedding of the lining of the gastrointestinal tract and bacterial proliferation in the colon, both of which contribute to the formation of stool.

Opioid-induced cognitive dysfunction can be a problematic adverse effect of opioids. A variety of opioids such as morphine, hydromorphone, and meperidine contain active metabolites that can cause excessive sedation, cognitive slowing, hallucinations, delirium, and seizures. These active metabolites, such as morphine-3-glucuronide, bind to opioid receptors in the brain. The concentration of these metabolites is affected by opioid dose, length of treatment, dehydration, and renal failure. The first steps in treating neurotoxic adverse effects without compromising pain relief are to (1) change the type of opioid that is being administered (opioid rotation), (2) hydrate the patient to enhance excretion of the drug and its metabolites, and (3) provide appropriate support to the patient and the family. In rare cases in which severe agitation, hallucinations, or delusions develop, haloperidol may be required.

Rotation of opioids is a safe and reliable method of alleviating symptoms in patients who develop opioid-induced neurotoxicity, although the ideal alternative opioid has not been determined. If the patient is taking morphine, a trial of hydromorphone, oxycodone, or fentanyl is usually effective. The dose of the second opioid should be determined according to guidelines that determine an equianalgesic ratio.

Other less common adverse effects resulting from opioid use include sweating, pruritus, urinary retention, and pulmonary edema. Respiratory depression is a rare and serious complication of opioid use, especially when it occurs in patients with no previous history of opioid use who have not developed tolerance to the respiratory depressant effect of the drug.

Pain in Special Situations

Incidental Pain

Incidental pain is sudden and severe pain provoked by special maneuvers such as swallowing or movement. An increase in opioid dose during episodes of incidental pain may result in excessive sedation after the pain episode has subsided. In such cases, attempts should be made to increase the local control of pain with the use of techniques such as radiation therapy, orthopedic procedures, and neurosurgical procedures.

Neuropathic Pain

Neuropathic pain is usually caused by damage to the nerves from direct tumor effect or its treatment. The pain can be burning or shooting. Neuropathic pain responds less to opioid therapy than does somatic or visceral pain, although it is generally alleviated by opioids to some degree. These patients frequently require the administration of adjuvant drugs in addition to opioids. The most commonly used drugs are tricyclic antidepressants, gabapentin, carbamazepine, clonazepam, baclofen, and corticosteroids.

Mucositis

Mucositis in patients with cancer of the head and neck usually results from the effects of chemotherapy, radiotherapy, or both. Pain is usually moderate in severity and the condition is self-limited in most cases, although rarely, pain can be severe and dose limiting. Mouth ulcers lead to dehydration from infection and decreased oral intake, especially among neutropenic patients receiving chemotherapy. Rehydration, local antiseptics, and oral opioids can frequently control the condition, although in severe cases, intravenous opioids may be required.

Nonpharmacologic Interventions

Some patients have severe pain that does not respond adequately to pharmacologic intervention; others develop intolerable toxicity. In these patients, adjuvant nonpharmacologic interventions should be considered

(**Table** 34.5). Approaches such as transcutaneous nerve stimulation and physical therapy can be attempted in most patients because of their relatively limited adverse effects and low costs. Radiation therapy should be considered in patients with bony metastases. Single large fractions may be as effective as multiple fractions and may reduce the patient's discomfort as well as treatment costs.[37] In difficult pain syndromes, some anesthetic procedures performed by neurosurgeons, anesthesiologists, or pain specialists, such as cordotomy, rhizotomy, and different nerve blocks, may be helpful.

Table 34.5 Nonpharmacologic Methods of Treating Cancer Pain
Acupuncture
Anesthesiologic Anesthesiology procedures
Biofeedback
Cognitive–behavioral therapy
Hypnosis
Neurosurgery
Occupational therapy
Orthopedic surgery
Physical therapy
Radiotherapy
Relaxation techniques
Transcutaneous electrical nerve stimulation (TENS)

A number of psychological techniques can be very effective adjuvant treatments for enhancing pain control. These include relaxation therapy, cognitive therapy, biofeedback, and hypnosis.[38] These techniques can affect both the sensory aspects of pain and the psychological distress that many patients in pain experience. In addition, they tend to be of relatively low cost and free of adverse effects.

Cachexia–Anorexia

Until recently, cachexia was believed to be the result of an energy imbalance caused by the combination of increased energy consumption by the cancer and decreased energy intake due to tumor-related factors affecting the satiety center in the brain. Attempts to reverse cachexia associated with cancer by administering parenteral or enteral nutrients led to no significant improvement.[39] The emerging view of cachexia associated with cancer is summarized in **Figure** 34.2. A recent review describes the roles of cytokines such as tumor necrosis factor (TNF), interleukins 1 and 6 (IL-1, IL-6), and interferon-alpha. Long-term administration of these cytokines can cause many of the classic features of anorexia.[40]

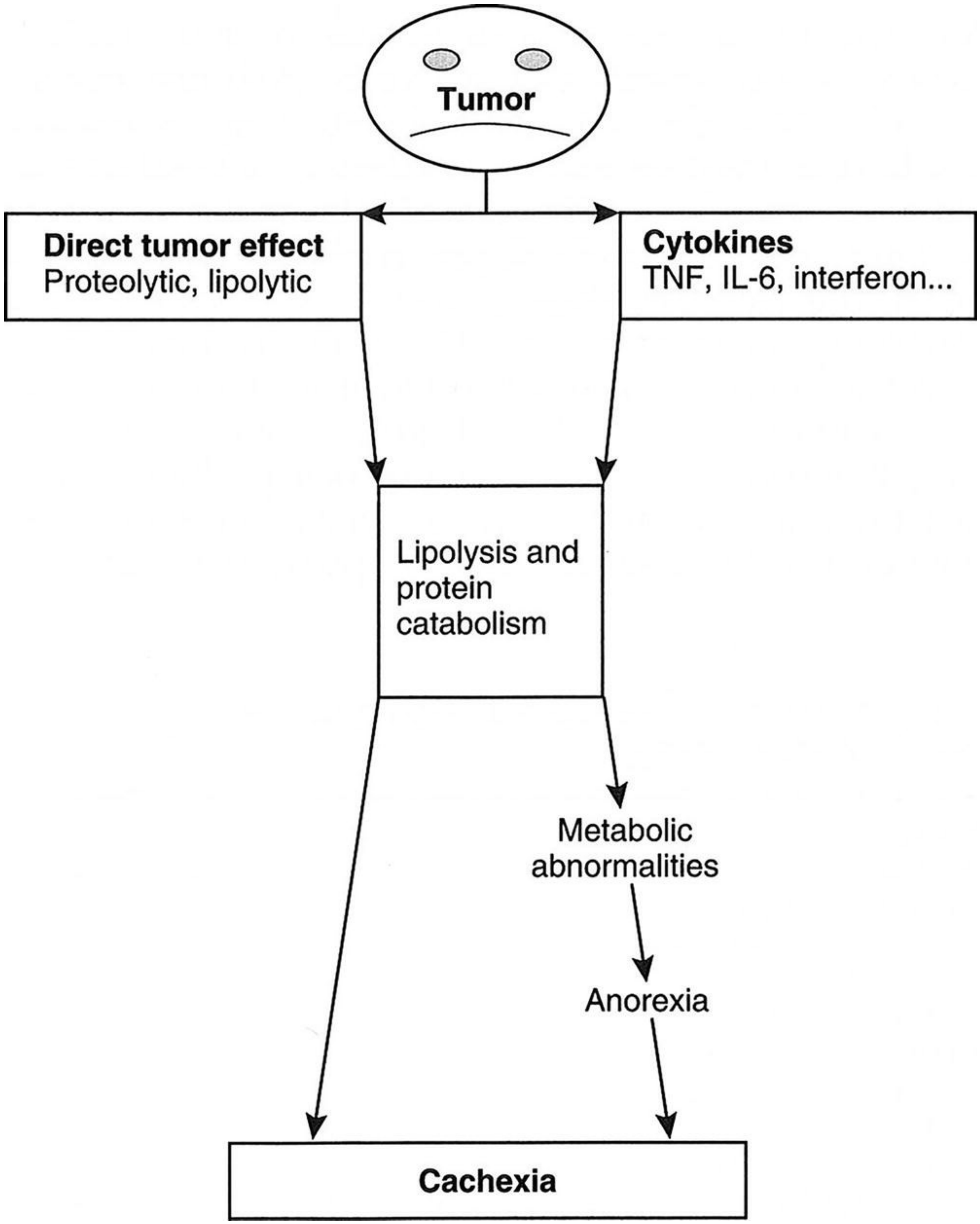

Figure 34.2. Mechanism of cachexia. (TNF, tumor necrosis factor.)

Anorexia is the most frequent distressing symptom in patients with

cachexia associated with cancer. Profound anorexia adds a nutritional deprivation component to the metabolic abnormalities. This deprivation is more severe in patients with dysphagia related to cancer of the head and neck. Anorexia is also worsened by nausea caused by tumor by-products, decreased gastric emptying, constipation, and pain medications. Moreover, patients with cancer of the head and neck can suffer from alterations of taste and smell that result in anorexia.

Management of Cachexia

One of the main challenges in the management of cachexia is defining a properly reasonable outcome for nutritional and pharmacologic interventions. A reasonable goal is to improve general comfort and ease the symptoms of anorexia, nausea, fatigue, and constipation.

Nutritional Approach.

Nutritional counseling may help improve daily caloric intake in many patients; however, it is unlikely to reduce weight loss in most patients. Adequate counseling of patients and their families about the metabolic mechanism of cachexia helps to alleviate the anxiety of family members that their relatives are starving to death.

Parenteral nutrition has no advantages over enteral nutrition and is more expensive. Enteral nutrition is safer and can be administered at home. Patients with cancer of the head and neck who have dysphagia or difficulties with mastication or swallowing may benefit from gastrostomy tube placement. This tube may also be used for administration of medications.

Pharmacologic Approach.

Table 34.6 summarizes the most useful drugs for the treatment of cancer cachexia. Promising research is under way to evaluate the possible beneficial effects of anticytokine therapies such as pentoxifylline, thalidomide, and melatonin. Multimodal interventions including anti-inflammatories, exercise, and nutritional improvement can help alleviate and/or reverse some of the effects of cachexia.[41]

Table 34.6 Drugs Useful for Treatment of Cachexia

Drug	Comment
Metoclopramide	Most effective in patients with chronic nausea and autonomic failure, and those on opioids.
Corticosteroids	Effect is short-lived (up to 1 mo). Suitable for advanced cancer. Significant adverse effects.
Megestrol acetate	Associated weight gain. Drug of first choice. Use associated with thromboembolism. Expensive.
Medroxyprogesterone acetate	Associated thromboembolic disease

Fatigue

Cancer-related fatigue is characterized by persistent and unusual tiredness occurring after usual or minimal effort, accompanied by an unpleasant anticipatory sensation of generalized weakness that is not relieved by rest. The three main mechanisms associated with fatigue are direct tumor effects, tumor-induced by-products, and medical complications, including anemia, paraneoplastic syndromes, and chronic infection. **Figure** 34.3 depicts the major causes of fatigue.

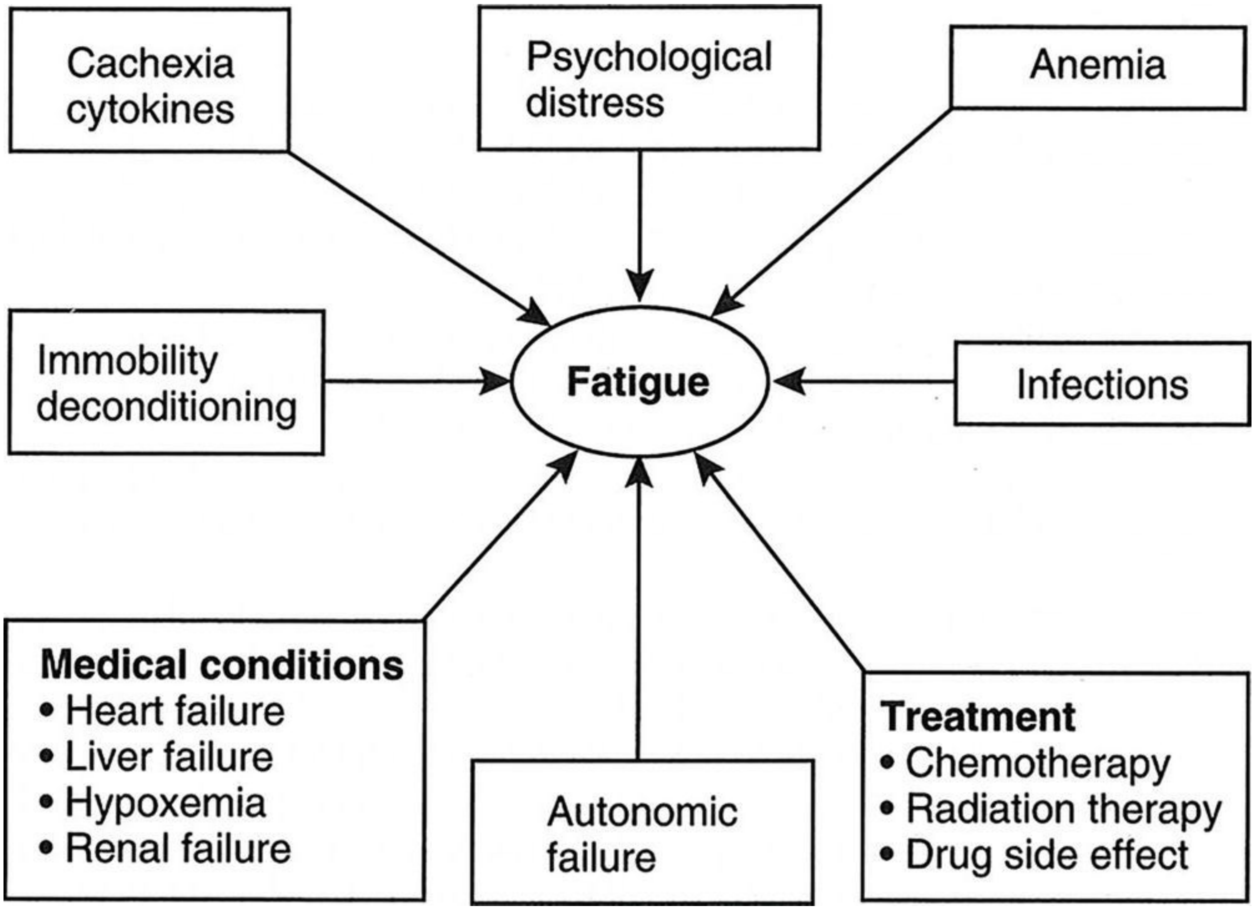

Figure 34.3. Causes of fatigue.

The relationship between fatigue and cachexia is complex; most patients with advanced cancer experience both. However, some patients with advanced cancer may have fatigue without malnutrition, whereas patients with conditions such as anorexia nervosa may experience severe malnutrition with no fatigue.

Management

Figure 34.4 presents a clinical approach to the management of fatigue. If specific causes can be identified, their correction will lead to significant improvement. General nonpharmacologic measures, such as adapting activities of daily living and providing physical therapy and occupational therapy, help in matching clinical function and symptom status with the expectations of patients and their families.[42] Counseling and appropriate pharmacotherapy may help patients in whom fatigue is exacerbated by an affective disorder such as anxiety or depression.

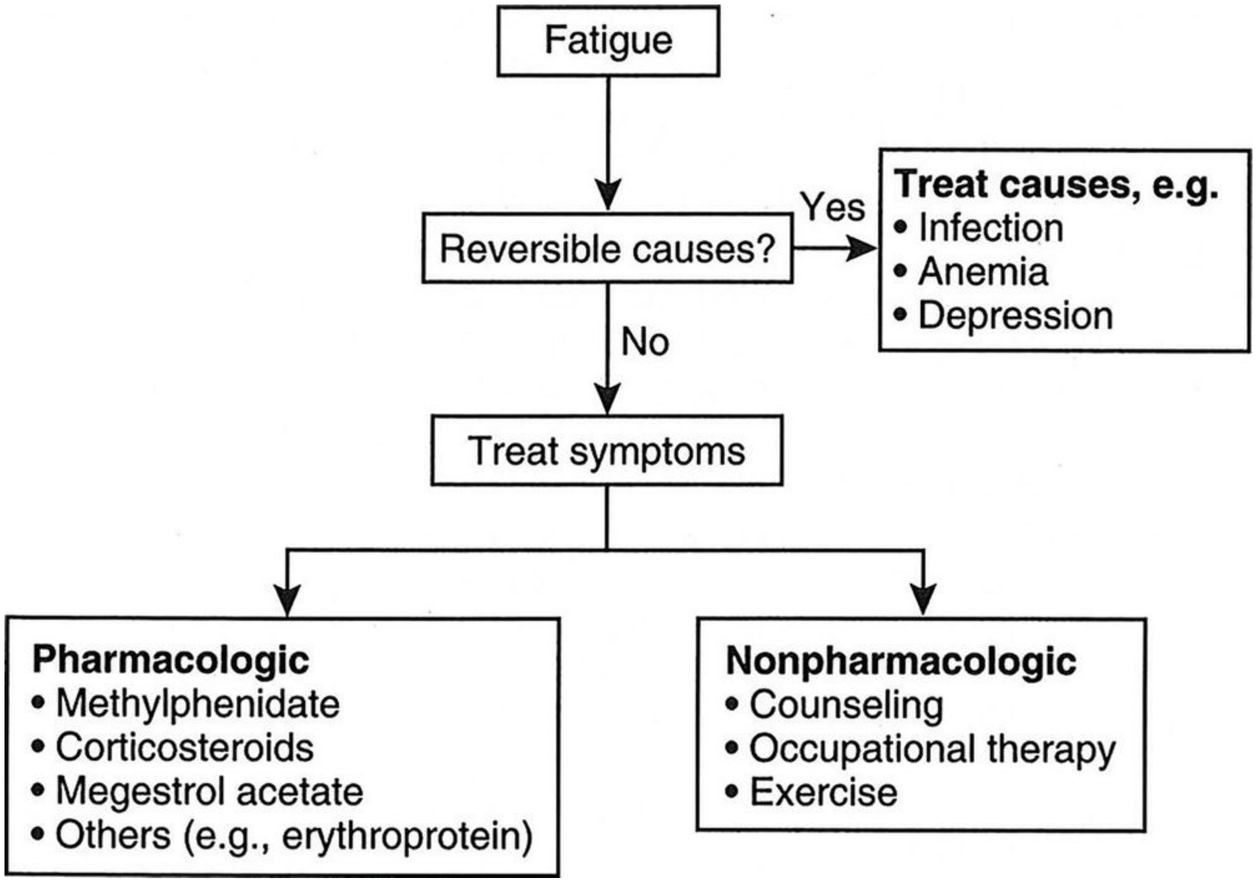

Figure 34.4. Algorithm for the management of fatigue.

Dyspnea

Dyspnea has been defined as an uncomfortable awareness of breathing. It is an unpleasant subjective sensation and cannot be measured by any physical abnormalities. **Figure** 34.5 summarizes the causes of dyspnea in cancer of the head and neck.

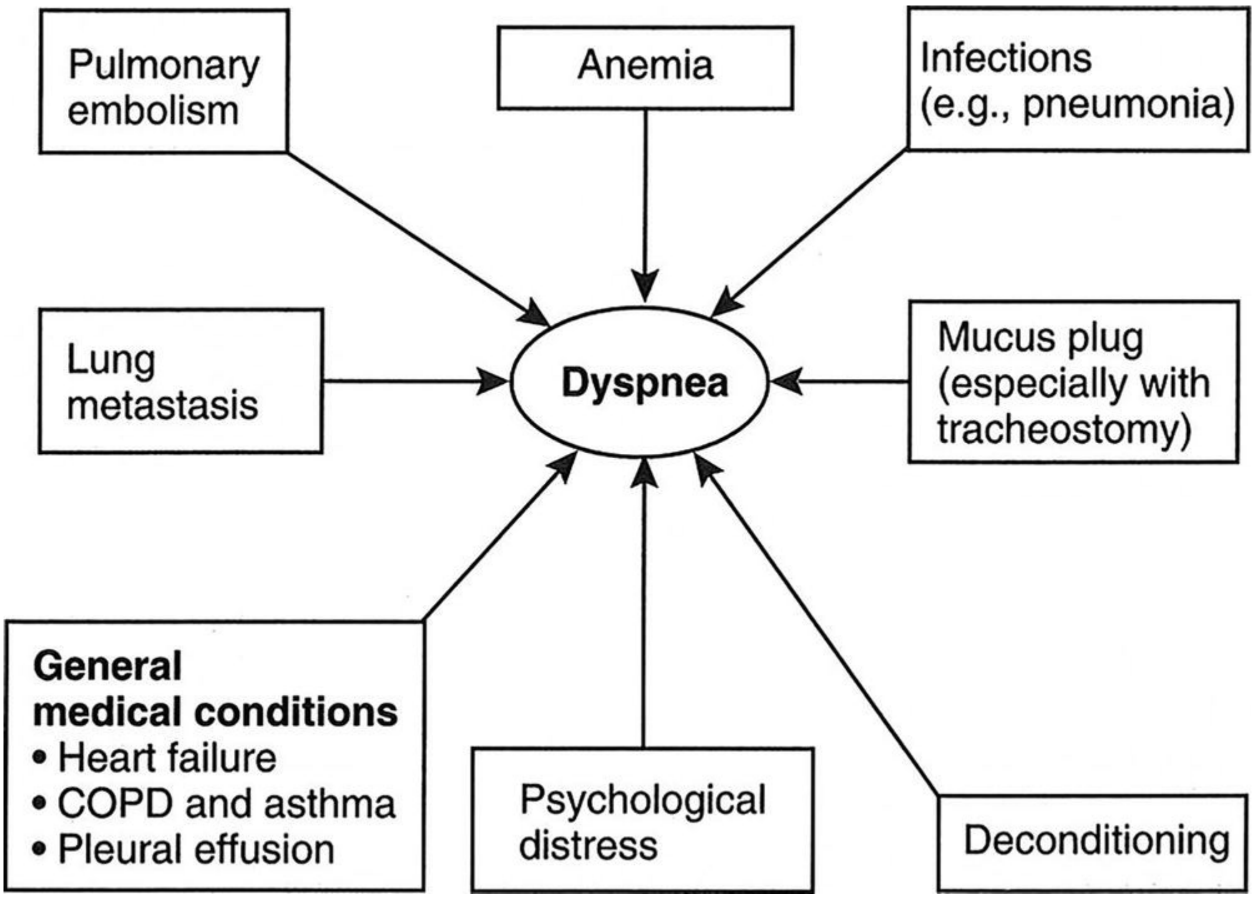

Figure 34.5. Causes of dyspnea in head and neck cancer. (COPD, chronic obstructive pulmonary disease.)

Patients with a tracheotomy have special problems related to accumulation of secretions and blockage of the stomal lumen due to enlargement of the tumor. The lumen can also be blocked during removal of the tracheotomy tube for cleaning. This can result in significant distress for the patient. In addition, caregivers often are stressed by caring for patients with tracheotomy.[43]

Many of the causes of dyspnea improve with treatment of the underlying condition, such as antibiotics for pneumonia, anticoagulation for pulmonary embolism, or blood transfusions for anemia. The symptoms of dyspnea are treated with oxygen, opioids, and behavioral strategies. Several randomized, controlled trials have shown that opioid therapy is beneficial for cancer dyspnea.[44] Corticosteroids are effective in the management of dyspnea associated with carcinomatous lymphangitis; they are also frequently used in the management of superior vena cava syndrome.[44]

Delirium

Delirium is the most common neuropsychiatric disorder, affecting ~85% of patients with advanced cancer.[45] Patients with delirium experience a combination of cognitive dysfunction, fluctuating levels of consciousness, reversal of the sleep–wake cycle (insomnia and daytime sleepiness), hallucinations (especially visual and tactile hallucinations), delusions, and other perceptual abnormalities. The condition is frequently misdiagnosed by clinicians as anxiety or insomnia, which may lead to certain interventions that worsen the delirium, such as prescribing benzodiazepines. Hospitalized elderly patients are particularly at risk, and clinicians should maintain a high degree of vigilance when patients experience sudden alteration in mental status. Family members are particularly helpful in identifying early changes in cognitive function and mood.

Figure 34.6 highlights the causes of delirium in cancer patients. Common causes of delirium in cancer patients include infection, adjuvant medications (especially corticosteroids and opioids), and electrolyte imbalance. Delirium is classified according to psychomotor activity as hyperactive (agitated), hypoactive (hypoalert), or mixed.[46] The hyperalert type of delirium is most common and tends to have the shortest duration and the best outcome.[47]

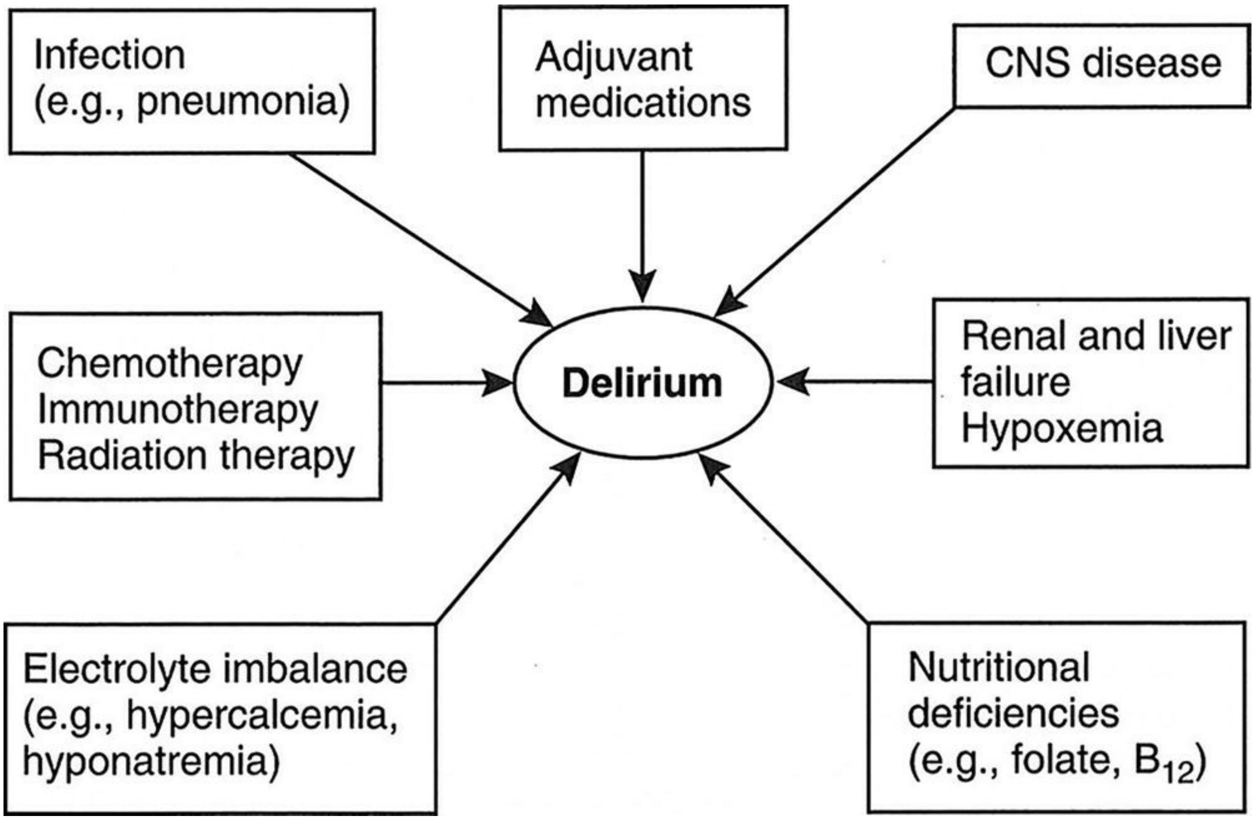

Figure 34.6. Causes of delirium in head and neck cancer.

A detailed history is of utmost importance in the diagnosis of delirium. Simple bedside tests, such as the Mini-Mental State Examination,[48] may be useful for screening patients suspected of having frank delirium, although such brief tools are not helpful in patients with focal lesions or mild to moderate cognitive dysfunction.[49] In cases of suspected but mild cognitive dysfunction, neuropsychological assessment may be useful. Neuropsychological evaluations are also useful in differentiating organic from functional disorders and in identifying early dementia unrelated to cancer.

The most important interventions in the management of delirium are to remove any contributing medications, to use opioid rotation, and to treat any contributing underlying medical conditions. Haloperidol can be used for symptomatic management of delirium. In about two-thirds of patients, delirium can be reversed and patients return to their baseline level of mental function.[50] Patients treated with haloperidol tend to have a shorter duration of this distressing state.[47]

Cannabinoids and Medical Marijuana

Cannabis has been used in medicine for more than 2,000 years. The interest in the potential medical effects of these compounds decreased after it became illegal. In recent years, the interest in cannabis has increased since the discovery of an endocannabinoid system. Many countries around the world have legalized the use of marijuana and other cannabinoid products both for medical and nonmedical reasons.

Cannabinoids have antiemetic effects that are mild as compared to those of the currently available potent antiemetic agents for chemotherapy-induced vomiting.

It has limited effects on appetite. There is stronger evidence regarding the role of cannabinoids for pain, particularly neuropathic pain.

The main limitations of these agents are the significant CNS side effects, especially highly debilitated patients who are also receiving opioids and other drugs. It has an addictive potential that is comparable to that of benzodiazepines but lower than the addictive potential of opioids, alcohol, or tobacco.

At the present time, there are limited indications for the use of cannabinoids in palliative care. More research is needed to better characterize the potential efficacy of these agents as adjuvants in the management of refractory pain and perhaps in selected cases of refractory emesis.[51]

SUMMARY

Patients with cancer of the head and neck suffer from multiple devastating physical and psychological symptoms. Pain, fatigue, cachexia, dyspnea, delirium, and psychological distress are precipitated by cancer and cancer treatment. These symptoms worsen the quality of life of patients with cancer of the head and neck and complicate their treatment. A history of alcoholism or poor psychosocial support may further complicate care. Multidimensional assessment of cancer-related symptoms is essential in helping to avoid complications, in providing early interventions, and in helping the patient and family cope better with the disease and its treatments. Palliative care, which can result in the provision of successful multidimensional care to patients with cancer of the head and neck and their families during the complete

course of the disease, should be integrated early in the trajectory of the illness.

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35 Quality of Life in Head and Neck Cancer

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INTRODUCTION

Cancer of the head and neck (HNC) and its treatments are associated with considerable burdens. Traditional clinical endpoints such as tumor control and survival provide little indication of the marked changes that patients experience in their day-to-day lives. Efforts to understand these challenges have become a more central concern. Thus, over the past few decades, health-related quality of life (QOL) has been recognized as a salient endpoint in clinical trials. Information about QOL outcomes is also important in clinical care. This information helps to inform patients and their families about what to expect during the course of care and facilitates decision making among treatment options. QOL data also assist clinicians in identifying common problems that must be monitored over time and inform the development of more effective screening and intervention services.

QOL research in HNC has grown dramatically over the past 20 years.[1,2] This chapter reviews some of the recent work in this area. We summarize some of the major difficulties that confront HNC patients at different phases of treatment and recovery. We review some of the important clinical and personal factors that may influence QOL outcomes. We examine interventions developed to enhance QOL among HNC patients. We discuss methods to assess QOL, and finally, we consider future directions for this field.

SYNOPSIS OF QOL CHANGES

HNC confronts patients with multiple challenges. Common concerns include disconcerting changes in functional capacity, disruption in daily roles, and uncertainty about the future. Patients may struggle with increased dependency on others and a diminished sense of control over their lives. The difficulties that patients experience are colored in part by the particularities of tumor site, treatment modality, and phase in the trajectory of illness.[3] During the initial period of active treatment, for example, patients must manage an array of acute toxicities.[4,5] Notwithstanding advances in treatment, symptom burden has become more pronounced with the move toward more aggressive, multimodal treatment approaches for individuals with advanced disease. The sequelae of illness and treatment may affect basic aspects of day-to-day functioning, including speaking, eating, respiration, and sometimes facial appearance— areas that play a fundamental role in social interaction and personal identity.

As patients transition from active treatment to long-term survivorship, other challenges may become more prominent.[3] These may include difficulty reestablishing normal routines,[6] fear of recurrence,[7] and sexual or social concerns.[8] Patients may need to adapt to a range of persistent or late effects (e.g., fatigue, xerostomia, dysphagia, dental complications, etc.).[4,9,10] Some are discouraged by ongoing limitations with eating or communicating. Others may struggle with recovery from nicotine or alcohol dependence, which have elevated prevalence rates in this population.[11] Finally, individuals who develop recurrence or disease progression are confronted by a new set of demands, as they cope with more pressing existential issues, intensified symptom burden, and complex end-of-life care decisions.

Aside from the impact on the patient, HNC creates major complications for the family as well.[12] Family members must accommodate multiple medical appointments and complicated caregiver tasks. Typical roles and responsibilities must be rebalanced. The burden on family caregivers has been further intensified by cost-driven changes within the health care system, including trends toward shorter hospital stays and increased home care. Traditionally neglected in both research and clinical care, family members recently have begun to receive greater attention. Studies suggest that partners often experience levels of distress that are comparable to[13] or greater than that of the patient.[14,15] Poorer communication between the spouses (e.g., less self-disclosure, greater efforts to hide from the partner one's concerns about

the illness) has been tied to greater levels of distress.[16]

QOL CHANGES DURING INITIAL TREATMENT AND RECOVERY

Patients in the initial phase of diagnosis and treatment may experience adverse changes in multiple domains. Longitudinal studies usually depict a characteristic deterioration in physical, role, and social spheres of functioning over the first few months; these changes unfold along with a series of more specific head and neck (HN) symptoms, including problems with swallowing, social eating, speech, HNC pain, xerostomia, sticky saliva, altered sensation, and nutritional deficits.[10,17–22] As expected, the most pronounced level of deterioration occurs in the acute treatment interval, followed by a gradual improvement (for survivors) over the course of the first year. By that point, many symptoms have returned to baseline (i.e., pretreatment) levels. Notably, however, clinically meaningful deficits remain in many areas. Protracted problems often include xerostomia, dysphagia, eating difficulties, speech problems, sticky saliva, fatigue, and diminished physical functioning.[10,17–22] Observers often highlight the encouraging improvements in global or general QOL, but these gains should not eclipse attention to residual concerns.

Aside from the adverse changes in physical functioning that emerge during active treatment, patients may experience difficulties in psychosocial well-being as well. Many report clinically meaningful levels of emotional distress. Prevalence estimates have varied widely across studies, due in part to methodological considerations (e.g., differences in measures, cutoff scores, and times of assessment). More rigorous studies have used diagnostic interviews instead of self-report questionnaires to evaluate psychosocial morbidity. Rates of major depression have ranged from 17% to 29% among patients assessed during the first year after diagnosis[23–25]; these estimates are notably higher than rates for the general US population. By way of comparison, these estimates are also somewhat higher than those derived from a recent meta-analytic review involving patients with diverse types of cancer and varying times of assessment.[26] These findings assume additional urgency because depressive symptoms have been associated with increased risk for malnutrition and poor adherence among HNC patients[27],28 and with

increased hospitalizations, poorer health behaviors, and diminished immune function in other patient groups.[29–31] Aside from depression, patients may experience other psychological difficulties as well (e.g., posttraumatic stress symptoms, adjustment disorder, etc.). Unfortunately, psychosocial morbidity is notably underdetected and undertreated in oncology settings.[32–34]

QOL CHANGES DURING LONG-TERM SURVIVORSHIP

Growing attention has focused on the experience of HNC survivors evaluated over the longer term, 3 to 5 years after diagnosis.[1] What challenges emerge during posttreatment survivorship? In contrast to the notable shifts in QOL that characterize the acute treatment period, subsequent changes over time are more limited. Several longitudinal studies[17,35–37] suggest stable or modestly improved global QOL, along with protracted problems in specific areas, including, for example, disrupted physical and role functioning, diminished taste and smell, xerostomia, sticky saliva, and dental concerns. At 3 to 5 years, these difficulties remained more burdensome than they had been at diagnosis. However, other areas seemed to improve compared to their pretreatment levels, such as emotional functioning and depressive symptoms.[17,36,37]

Other studies have compared the experience of HNC survivors to that of healthy comparison groups, 3 years or more after treatment. As one might expect, HNC patients (with diverse anatomical sites and treatment histories) report greater problems with HN symptoms (e.g., trismus, xerostomia, diminished taste and smell) relative to age-matched population norms.[35,38] However, findings regarding broader aspects of QOL (e.g., disrupted physical functioning, mental health, and vitality) have varied across studies, with some showing extensive deficits[39,40] and others more narrow differences,[38,41,42] compared with healthy individuals. Overall, it appears that many long-term survivors manage well but experience persisting effects in specific domains. Helping individuals adapt during the phase of survivorship is becoming a stronger priority for oncology teams.

CLINICAL CHARACTERISTICS

ASSOCIATED WITH QOL

QOL outcomes are influenced by basic characteristics of the illness and treatment, though these findings are not as consistent as one might anticipate. In view of the limited number of randomized studies, it is often difficult to disentangle the effects of one clinical characteristic from another (e.g., disease stage vs. treatment modality). Generally however, patients with advanced disease tend to fare more poorly than do those with less disseminated disease,[17,19,24,43–47] though this is not always the case.[20,22] Individuals undergoing more aggressive, multimodal treatment usually have greater difficulties than do those who receive single-modality treatment,[17,48,49] and similarly, those who receive more extensive surgical[5,50,51] or radiotherapy[46] interventions experience greater problems than do patients treated with more limited protocols.

QOL is also shaped by the specific treatment regimens that patients receive. An important objective is to determine whether advances in therapeutic approaches are associated with meaningful improvements in daily physical and psychosocial functioning. Some of this work has focused on innovations in radiotherapy strategies. Intensity-modulated radiotherapy (IMRT), which is designed to target the tumor bed while more effectively limiting the exposure of surrounding radiosensitive tissue, has been widely adopted. Several nonrandomized studies suggest that IMRT is associated with enhanced QOL outcomes relative to conventional radiotherapy[52–55] (for a review, see Tribius and Bergelt[56]). For example, in a matched-pair comparison study (average follow-up of 23 months), patients treated with IMRT fared better with respect to physical functioning and several HN morbidities (e.g., xerostomia, sticky saliva, trismus, pain, swallowing), compared with those who had received conventional radiotherapy.[52] However, QOL benefits have been less pronounced in the few randomized studies conducted thus far. These investigations have confirmed improvements in objective endpoints such as salivary flow and clinician-rated xerostomia, but noted less consistent differences in patient-reported outcomes.[57–59] Few of these investigations have had adequate statistical power to detect QOL differences; thus, more definitive conclusions await further research.

Other investigations have examined QOL changes associated with

advances in surgery. Some of these efforts have evaluated changes in reconstructive techniques. For example, with innovations in microvascular surgery, the use of free flaps has become more prominent than the use of pedicled pectoralis major myocutaneous flaps, which had been a mainstay in reconstruction for patients with cancer of the oral cavity. Free flaps require more extended time in the operating room and more specialized skills, but there are fewer complications, briefer hospitalizations, and lower costs.[60,61] Some studies have pointed to long-term improvements in QOL, such as less pain and enhanced appearance, speech, and emotional functioning among oral cancer survivors (assessed on average more than 3 years after surgery) who underwent reconstruction with free flaps, relative to those who received pectoralis major pedicled flap reconstruction.[62,63] Recently, there also have been efforts to compare different approaches to free flap reconstruction. There are preliminary indications that anterolateral thigh perforator flaps are associated with more favorable QOL outcomes, including better appearance, improved social functioning, and fewer shoulder problems, compared with radial forearm free flaps (at an average of 3 years after surgery).[64] However, caution is required in interpreting each of these studies, because none involved randomized designs and none accounted for imbalances in clinical or demographic characteristics between the reconstruction groups.

Another approach with important QOL implications involves endoscopic surgery. Endoscopic procedures, which are usually performed with a CO_2 laser, have become more common as an alternative to open surgery or radiotherapy, especially for early-stage glottic cancer. Thus far, studies have found few differences in QOL outcomes for endoscopic surgery compared with radiotherapy in this patient group[65–67] (see Spielmann et al.[68] for a review). Findings are tentative however because these were small nonrandomized investigations, which evaluated mostly long-term survivors, who may no longer experience the same sequelae that were evident earlier in care; moreover, most of the studies were characterized by clinical or demographic differences between treatment arms. Endoscopic approaches are also used to treat selected patients with more advanced disease.[69] A recent nonrandomized study[70] focused on patients with hypopharyngeal cancer, assessed closer in time to the end of treatment (average of 10 months). Those who received transoral laser surgery demonstrated significantly better outcomes compared with the open surgery group (e.g., improved emotional

and social functioning, speech, social eating, social contact, sensation, dentition), as well as better outcomes than the chemoradiation group (e.g., fewer problems with dry mouth, social eating, social contact). Results should be interpreted conservatively in view of group differences in tumor stage and time since end of treatment. We anticipate that QOL research regarding endoscopic surgery and transoral robotic surgery will continue to expand over the next few years.

Another area that has garnered continued interest and debate involves comparisons across different treatment modalities. Considerable attention has been devoted to organ preservation protocols, such as chemoradiation, as an alternative to extensive resection, in the hope that symptom burden and QOL can be improved without compromising locoregional control or survival. Most of these efforts have focused on patients with locally advanced HNC, including advanced oropharyngeal or laryngeal cancer. Findings are inconsistent. They are also difficult to interpret in the absence of randomized trials. Nonetheless, it is clear that the chemoradiation has difficult toxicities of its own (consistent with the oft-cited observation that organ preservation is not synonymous with organ function). In general, findings suggest that each treatment modality is associated with characteristic symptoms and functional limitations (some of which are distinct and some of which overlap with those of other treatments), so selection among therapeutic options remains a complex process for many patients with advanced disease.

For example, among advanced oropharyngeal cancer survivors (assessed an average of 4.7 years after the end of treatment), the group who had been treated with concurrent chemoradiotherapy reported significantly greater difficulties with a number of symptoms, including trismus, dental concerns, xerostomia, and sticky saliva, than did those who had received surgery and postoperative radiotherapy.[9] On the other hand, the surgery group had more problems in other areas (i.e., fatigue, pain, swallowing, social eating, and social contact). Similarly, at 1-year follow-up, Oates et al.[43] reported relatively greater deterioration for the chemoradiation group in some domains (e.g., trismus, dentition, swallowing, sexuality, feeling ill), but more pronounced deterioration for the surgery and postoperative radiation group in other domains (e.g., cognitive functioning, fatigue, pain, diminished sensation). In a very small subgroup analysis of survivors of advanced cancer of the oropharynx, findings hinted at clinically meaningful benefits for the

radiotherapy group, compared with the surgery and postoperative radiotherapy group, in several areas (e.g., physical, social, role, and emotional functioning, pain, dyspnea).[71] However, interpretations are limited by considerable imbalances between the groups in time since treatment. In contrast, another subgroup analysis of advanced oropharyngeal cancer survivors (average follow-up of 3.7 years) tentatively suggested clinically meaningful advantages for the surgery group (e.g., global, social, and cognitive functioning, nausea, reliance on analgesics), though once again the sample was very small.[72] Other investigations of intermediate- to long-term survivors of advanced cancer of the oropharynx reported few group differences.[40,73] Ultimately, of course, more definitive information about differential effects on QOL will require large, multicenter randomized trials.

PERSONAL CHARACTERISTICS ASSOCIATED WITH QOL

Relationships between demographic variables and QOL outcomes have been inconsistent. Women have reported poorer QOL[17,46,47] or emotional well-being[17,74,75] in some studies but not others.[44,76,77] Older patients sometimes demonstrate better psychosocial well-being[42,77] but poorer physical functioning[17,42,47] than do their younger peers, though again many studies have reported no differences.[44,74–76]

Aside from clinical or demographic factors, the personal resources that participants bring to the illness appear to have a salient effect on QOL.[3] Thus far, these variables have received greater research attention in other types of malignancies, but they are beginning to draw closer scrutiny in the HNC literature. For example, in longitudinal studies, higher levels of optimism about life (dispositional optimism) predicted better global, role, and cognitive functioning[78] and improved emotional well-being[79] after treatment. In relatively large cross-sectional analyses, greater optimism was related to improved physical, functional, and social well-being,[80] whereas pessimism was tied to poorer physical and social functioning.[81] Coping strategies appear to be important as well. Several studies suggest that participants who engage in counterproductive responses, such as self-blame, avoidance, wishful thinking, catastrophizing, or passive coping, experience greater emotional

distress and poorer QOL.[76,82–86] It would be helpful to extend this work from cross-sectional investigations to longitudinal studies and to differentiate more clearly between cancer-specific coping efforts[82,83] versus more general coping strategies.

QOL is also colored by the social and cultural contexts in which patients live. Social support is thought to be a critical resource for cancer patients. A few longitudinal studies reported that perceived support prior to treatment predicted subsequent improvements in HN symptoms[87] and depression.[75] Similarly, several cross-sectional studies suggested that greater perceived social support was related to more favorable outcomes, such as enhanced medication adherence,[88] improved speech,[89] reduced social disruption,[89] and greater emotional well-being.[23,74,89] However, some investigations have reported null findings, especially at intervals further removed from the demands of active treatment.[42,90] There are multiple dimensions of social support, which may have complex relationships with QOL outcomes.[23,81] Investigators have begun to explore some of these other facets of support among HNC patients (e.g., received vs. available support[75]; open communication vs. protective buffering[16,91]; affirming vs. undermining relationships), which should reveal a more nuanced picture.

Identifying other modifiable factors that contribute to risk or resilience for QOL difficulties is an important priority area for future research in HNC. Findings may have significant implications for clinical care, because these factors can be targeted in interventions to improve adaptation.

EMERGING AREAS OF RESEARCH

A number of important outcomes have received minimal attention in standard QOL assessments, but are now drawing increased interest. These issues are rarely discussed in clinical encounters despite their appreciable impact on daily life. Many patients struggle with marked fear of disease progression or recurrence.[7] These concerns vary in intensity, but are evident across the trajectory of illness, from initial diagnosis and active treatment[92] through long-term survivorship.[92–95] We anticipate that these concerns may be especially pronounced in HNC, which is associated with a high risk for relapse. Interestingly, however, fear of recurrence seems less rooted in

objective prognostic factors than in patient characteristics, such as younger age,[93,95] greater generalized anxiety or distress,[92,93,95] and lower dispositional optimism.[92]

Other patients experience a sense of stigma or shame regarding their illness.[96] Despite advances in surgery, cosmetic changes are a significant hardship for some individuals. Facial disfigurement, whether rated by the patient or by an observer, has been tied to greater emotional distress, social discomfort, and isolation.[23,97,98] Individuals who are more confident in their ability to manage social situations (i.e., higher in social self-efficacy)[97] or who perceive stronger social support[23] may be buffered from these difficulties. Other patients may feel stigmatized because of overt functional deficits associated with their illness (e.g., eating or speech problems) or because of the role that health practices may have played in its etiology (e.g., nicotine or alcohol dependence or human papillomavirus (HPV) infection). Stigma has been related to greater depression and lower well-being in a number of studies.[96,98,99]

Disruptions in sexual well-being are another area of concern for many cancer survivors. In recent studies, roughly one-third to one-half of HNC patients at varying phases of recovery reported difficulties with sexual interest or sexual satisfaction.[8,19,43,100–102] Most of these investigations included only very brief measures. Thus far, few studies have examined more comprehensive aspects of sexual function among HNC patients[102] or compared findings to those of age-matched healthy individuals. More detailed studies are needed to help clarify the scope of these difficulties and their risk factors.

Most QOL research has focused on identifying burdens and morbidities. It seems clear, however, that some patients experience unexpected positive life changes as well as negative ones. They discover that life has been enriched in some ways (e.g., deepened relationships, strengthened spirituality, a renewed sense of appreciation or purpose), even if depleted in others. An exclusive focus on QOL deficits may obscure the complexities of patients' responses to the illness. Positive changes in the aftermath of adverse events have been referred to as posttraumatic growth, stress-related growth, or benefit finding. Efforts to understand these experiences have given rise to several coherent theoretical models[103,104] and a large empirical database.

Within the HNC literature, a few studies have begun to explore factors that might contribute to perceived growth. Consistent with findings in other malignancies, greater optimism[105–107] and active coping or positive reframing[105,106] have been tied to increased perceived growth. At the same time, stronger challenges (i.e., perceived disfigurement, stressful events), which are thought to prompt a reevaluation of one's life, may be related to perceived growth as well.[98] Further research in this area may help clarify the nature, durability, and correlates of positive changes in response to HNC.

Other important areas[1] that have received surprisingly little attention in HNC research include adherence,[88] decision-making processes, survivorship plans, and end-of-life care.[108]

QOL INTERVENTIONS

Treatment for HNC requires interdisciplinary care. Greater recognition of the QOL difficulties that patients experience has prompted a growing emphasis on provision of psychosocial support services. Intervention research in HNC is at an early stage of development. As yet, few randomized trials have been completed. A recent meta-analytic review of randomized studies concluded that there was insufficient evidence available to substantiate the use of psychosocial interventions for HNC patients,[109] a conclusion that seems unsurprising given the small number of studies included and the diversity of intervention strategies and measures that were employed. Nonetheless, the landscape is shifting. Some additional innovative projects have emerged, and others are in progress.

One of the largest randomized studies completed thus far examined the value of a nurse-led intervention, which encompassed six individual counseling sessions over the course of the year following completion of HNC treatment.[110] This broad-based, manualized program included ongoing screening for depression, assistance with medical symptoms, and counseling or skills training for psychosocial difficulties. At 1 year following completion of cancer treatment, the intervention group (n = 103) demonstrated significantly reduced depression scores (the primary outcome) relative to the usual care control group (n = 102). The same beneficial effects were evident for the subgroup of patients who were classified as clinically depressed at enrollment. The intervention group also reported greater improvements in

several QOL domains (e.g., emotional functioning, trismus, pain, swallowing).[111] A similar pattern of benefits was evident at the 18-month follow-up, though by 2 years after cancer treatment, there were few significant differences.

Another study sought to address problems with smoking, alcohol use, or depression, among patients who screened positive for these difficulties.[112] Participants were randomized to a usual care condition (a single assessment, which included educational handouts and referrals), or a cognitive–behavioral intervention, which included 9 to 11 telephone sessions and a workbook. Six months after enrollment, those in the intervention arm (n = 93) reported significantly greater improvements in smoking cessation, relative to those in the control arm (n = 91). There were no group differences in alcohol use or depression. Other investigators compared two treatment approaches for patients with high levels of posttraumatic stress disorder (PTSD) symptoms, anxiety, or depression.[113] Patients were randomized to six sessions of either cognitive–behavioral treatment (CBT) or nondirective supportive counseling. Participants in both conditions showed improvement over the course of 12 months, and there were no significant group differences, though the proportion of patients with clinically meaningful symptoms seemed lower in the CBT condition.

Several nonrandomized studies also provide hints about the potential value of psychosocial interventions for HNC patients. One project focused on a nurse-led psychoeducational program for patients who had completed cancer treatment.[114] Individuals were eligible for this project if they exceeded cutoff values for distress. Participants elected to receive usual care, or chose two to six sessions of individualized counseling at home, supplemented by homework, to address psychosocial difficulties. At the end of treatment, the intervention group (n = 25) demonstrated significantly greater improvement in depression, anxiety, psychosocial problems, and QOL scores compared with the control group (n = 29); most of these improvements were maintained at a 3-month follow-up. Another nonrandomized investigation evaluated a coping skills program for patients who had completed cancer treatment.[115] Participants chose their preferred format for the brief intervention: two to three individual sessions; two to three group sessions; or a workbook, with access to a clinician as needed. At the end of the intervention, multivariate analyses indicated that those who received the coping program (in any of the

three formats, *n* = 45) experienced significantly better global QOL and marginally better depressive symptoms, compared to a control group (*n* = 56). There were no group differences in other dimensions of QOL or in anxiety.

On the other hand, few benefits were evident in another nonrandomized study that evaluated a support program for patients during treatment and early survivorship.[116] Patients in the intervention arm were offered weekly individual visits with a nurse and a dietician during oncology treatment; sessions were subsequently provided monthly for 6 months and then at 1- and 3-year follow-ups. There were no improvements on multiple measures of distress or QOL for the intervention patients (*n* = 52), relative to control patients (*n* = 92) who lived further away from the facility and had been matched on several variables (age, stage, gender, and anatomical site). Indeed, the intervention group seemed to fare worse on some measures. Finally, more ambiguous results emerged from a nonrandomized investigation of a nursing intervention.[117] Intervention patients received six sessions with a trained nurse over the course of year following completion of cancer treatment. Nurses provided medical checks, screened for psychosocial problems, and offered advice and support. Prior to beginning the program, intervention patients reported greater problems than did those in the usual care control group—they scored significantly worse on most psychosocial and QOL measures. By the 6-month and 1-year assessments, the intervention patients (*n* = 80) had improved to the level of the control patients (*n* = 80). Thus, they showed stronger changes from baseline on a wide number of scores (especially at the 6-month assessment). These findings hint at intervention-related benefits, but of course, other interpretations cannot be ruled out (e.g., regression to the mean).

In sum, results have varied across studies—in general, stronger findings appear to be associated with theoretically informed, skills-based interventions administered by carefully trained clinicians, targeting patients with elevated symptoms. The optimal “dose” for different interventions has yet to be clarified, but most of the projects studied thus far have included relatively few sessions.

ASSESSING QOL

Assessment of QOL is grounded in some basic principles.[1,2] Health-related QOL is construed as a multidimensional construct—it encompasses patients' perceptions of their status across several domains of functioning, including physical, emotional, social, and spiritual well-being. Thus, the use of global or summary measures of QOL tends to obscure important differences in specific areas. QOL is typically viewed as a broader, more comprehensive concept than related outcomes such as performance status, toxicities, or symptomatology. It is grounded in the individual's personal appraisals; these perceptions are not readily captured by proxy ratings from clinicians or family members, which tend to correlate poorly with patient self-report.

Over the past 25 years, there has been a major focus on developing psychometrically sound measures of QOL for use in HNC. A large toolbox of validated instruments is available (for a review, see Ojo et al.[2]). None is ideal for use in all circumstances; rather, measures should be selected to accommodate the particular needs of the assessment.[118] Generic measures of health-related QOL (e.g., Medical Outcomes Study Short Form-36[119]) are useful in evaluating comparisons between HNC patients and healthy population norms or patients with other illnesses. Cancer-related measures (e.g., FACT-G,[120] EORTC QLQ-C30[121]) assess difficulties commonly encountered by oncology patients. In contrast, disease-specific measures (e.g., FACT-HN,[120] EORTC QLQ-H&N35,[121] University of Michigan Head and Neck QOL,[122] Head Neck Cancer Inventory,[123] University of Washington QOL questionnaire[124]) offer a more focused evaluation of problems that characterize that particular disease or tumor site. A common practice involves use of combined modules, which encompass both a general and a disease-specific measure,[118] in order to capitalize on the advantages of each (e.g., FACT-G and FACT-HN module or EORTC QLQ-C30 and EORTC QLQ-H&N-35).

HNC-specific instruments vary in their content domains, so instrument selection is sometimes based on the particular morbidities of greatest interest. Among other considerations, choices also may be driven by the need to ensure comparability across studies (when more widely used measures are more helpful than uncommon ones), the reliability of the measure (when multiple items in each domain may be more useful than single items), or sensitivity to change (when it is important to capture changes over time or treatment).

Investigators have also drawn on more narrowly targeted instruments, each geared toward a particular treatment modality (e.g., QOL-Radiation Therapy Index,[125] Neck Dissection Impairment Index[126]), HNC symptom (e.g., Xerostomia Questionnaire,[127] MD Anderson Dysphagia Inventory[128]), or anatomical subsite (e.g., FACT-Nasopharyngeal module[129]). Those who wish to assess specific psychosocial outcomes, such as emotional distress, fatigue, sleep disturbance, or sexual concerns, have a wide assortment of well-established measures from which to choose.

Recently, there have been some exciting trends in QOL assessment. One involves national efforts to develop a repository of refined measures (e.g., item banks) that can be used across a broad range of clinical settings and patient groups. For example, since 2004, the National Institutes of Health (NIH) Patient Reported Outcome Measurement Information System (PROMIS)[130] has generated a portfolio of abbreviated scales with strong psychometric properties. Using item response theory analyses, it has also expanded opportunities for use of Computer Adaptive Testing (an efficient, individualized assessment approach in which the next item administered is based on the patient's response to the previous item). Ultimately, programs such as NIH PROMIS, the NIH Toolkit, and the National Cancer Institute's Grid Enabled Measures (GRID) are expected to contribute to a common core of measures, allowing greater comparability across studies.

What does a number on a QOL questionnaire tell us?—the meaning of a score is not always apparent. Thus, another important development involves attempts to determine the clinical importance of QOL scores, instead of only their statistical significance. Several approaches have been used to enhance the interpretability of QOL findings. Population norms are available for some instruments, such as the FACT-G[131] and the EORTC-QLQ-C30.[132] Some investigators have sought to define thresholds or cutoff values, reflecting minimum scores that patients regard as acceptable.[133] Others have determined the meaning of differences in scores (i.e., the "minimal clinically important difference") by using clinical benchmarks (anchor-based methods[134]), the statistical properties of the score distributions (distribution-based methods[135]), or meta-analyses of scores from large groups of patients combined with the ratings of expert panels.[136] All of these approaches are intended to improve the practical, clinically meaningful level of information that QOL instruments can provide.

Thus far, the use of QOL assessments in routine clinical practice remains limited. Of course, the tools that are most helpful for rapid clinical screening and referral differ from those needed for comprehensive evaluation. Greater integration of patient-reported outcome measures into clinical care may be facilitated by selection of brief, symptom-focused, readily interpretable measures, perhaps administered by computerized systems that provide real-time feedback to clinicians.

CONCLUSIONS

Day-to-day life is altered in fundamental ways by HNC and its treatments. Efforts to evaluate these QOL challenges, to track changes over the course of illness, and to provide appropriate screening and intervention services are core aspects of patient-centered care. QOL research in HNC has been marked by significant advances in recent years. A growing database, based on validated instruments, has highlighted some of the physical and psychosocial difficulties that patients encounter. Studies have targeted more homogenous samples, capturing sequelae associated with specific treatments, distinct anatomical sites, and particular stages of disease. Longitudinal investigations, which illuminate patterns of deterioration and improvement over time, are becoming more common. Moreover, investigators have started to reach beyond traditional QOL endpoints to evaluate additional outcomes that are important to patients, such as fear of recurrence, stigma, sexual difficulties, and caregiver burden. Studies have begun to explore the possibility of positive life changes as well as negative ones. Research on screening and intervention is nascent but expanding. Furthermore, attention has been devoted to defining findings that are clinically meaningful instead of only statistically reliable.

As the field moves forward, some additional considerations would be important to address. Very few studies have focused specifically on the experience of individuals with HPV-related HNC or those with recurrent disease. Moreover, few have focused on patients from underserved ethnic/racial minority groups, or from rural areas, who may bring distinct needs and resources. Research directed toward these participants would make a welcome contribution.

Further progress will require attention to methodological concerns. For

example, most studies remain small and underpowered, so potentially meaningful findings may be missed. Multicenter collaborative investigations would provide greater prospects for ensuring adequate samples, especially given the high attrition rates that are characteristic among patients with a demanding illness. They would also provide greater opportunity to control for confounding factors, which are a common problem in HNC research. In addition, the great majority of QOL investigations in HNC are atheoretical. Research would be enhanced by drawing on appropriate theoretical frameworks to explore predictors of risk and resilience and to guide interventions.

Enhancing QOL for HNC patients is an important mandate. Continued developments in QOL research will make a significant contribution to the quality of care.

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36 Application of Advances in Endoscopic and Robot-Assisted Approaches to the Treatment of Head and Neck Cancer

Jason G. Newman Bert W. O'Malley Jr.

INTRODUCTION

The history of medicine has included some significant milestones. From the separation of philosophy and clinical medicine in the days of Hippocrates, to the understanding of the role of microorganisms in the creation of human illness, there are some concepts and tools that have literally changed how we understand and practice medicine. These individual changes have caused massive paradigm shifts, which first disrupt and then propel forward our approach to treating the human condition. Over the last 100 years, medicine has moved forward at a breakneck pace. Surgery has taken several big steps over this time frame. Open surgery, in the age of modern anesthesia, advanced imaging, and antibiosis, has become safe and effective in most cases. This has allowed us to concentrate on even further advances in the practice of surgery. Minimally invasive approaches and now even robotic approaches are becoming standard options in the management of many surgical diseases. In this chapter, we will review the history and discuss the evolving applications of both endoscopy and robotics in the field of head and neck cancer surgery.

HISTORY OF ENDOSCOPY IN OTOLARYNGOLOGY

Endoscopy within the field of otolaryngology has followed two separate but closely intertwined paths. On the one side is endoscopy to evaluate the larynx, and on the other, the sinonasal cavities. Although each of these anatomic regions has faced its own set of obstacles and techniques, what continues to keep them linked is the reliance on technology to access and operate in these tight spaces through natural orifices.

History of Sinonasal Endoscopy

In the 1970s, an Austrian physician, Walter Messerklinger, introduced the use of endoscopes in the performance of sinus surgery. Several of his students, including Stammberger and Kennedy, continued to advance the indications for the use of the endoscope within otolaryngology.[1] Initially, the endoscope was primarily used as a tool to aid in the medical management of inflammatory sinus disease. However, the endoscope quickly became the instrument of choice for management of surgical sinus disease. Over time, as descriptions of the anatomy, surgical techniques, and instrumentation began to evolve, the capacity to advance the frontier of the endoscope has grown.

Anterior skull base CSF leaks were among the earliest advanced procedures performed transnasally with an endoscope.[2] Creating safe techniques to separate the intracranial and sinonasal spaces was paramount in creating a safe and low-risk procedure. Initially, this involved the use of free mucosal grafts, adipose tissue, and nasal packing. In the 1990s, several authors described the use of the endoscope to assist in removal of tumors of the sinonasal and anterior cranial base, often with the combination of open and endoscopic techniques.[3] In 2001, Casiano et al.[4] reviewed the first series of purely endoscopic resection of esthesioneuroblastoma. Their success and the success of other authors led to a continued interest in the expansion of the use of this technique. Creation of hemostatic agents, finer and more angulated instrumentation, and techniques for closure of skull base defects were all results of these early surgical endeavors. Free mucosal grafting, inlay grafting techniques, and pedicled flaps have all played a role in the evolution of our surgical capabilities in this area. In addition, fine-cut CT and MRI scans, intraoperative navigation, and high-definition endoscopes have all allowed surgeons to address complex lesions more safely. Since these early studies, many surgical teams have gone on to describe large series of patients undergoing endoscopic resection of sinonasal malignancies.[5,6] Most recently,

the endoscopic endonasal approach (EEA) has been expanded to include options for management of tumors in areas other than the sinonasal cavity. This includes intracranial tumors, as well as tumors in the infratemporal fossa and pterygopalatine space. The sinonasal cavity has now, in many cases, become for the endoscopic approved corridor to the region of primary concern.

History of Laryngopharyngeal Endoscopy

At the same time as the early descriptions of endoscopy in the sinonasal cavity was first being described, Strong, Jako, Steiner, and others[7,8] began to develop the field of endoscopic laser surgery (ELS) for the larynx. This led the way to transoral laser microsurgery (TLM). Since that time, techniques and instruments have evolved to the point where almost all regions of the upper aerodigestive tract are accessible for surgical endoscopy and resection of tumors.

As is true with sinonasal endoscopy, endoscopy of the larynx required a continued expansion of the instruments, optics, and hemostatic methods to aid in its wider application. A variety of laryngoscopes, laryngeal microinstruments, specialized endotracheal tubes and suspension techniques have been designed to maximize the ability to visualize and safely operate in this tight space. The CO_2 laser was an important tool for the safe performance of this surgery, as both an instrument of resection as well as a hemostatic tool. Its long wavelength (10,600 nm) and other physical properties originally required that it be delivered via a microscope-mounted beam splitter (or a direct mounted beam) into the surgical site. Until recently, the use of the CO_2 laser has required a direct line of site from the laser emitter to the surgical site, often creating significant difficulty in both visualizing and manipulating the tumor. Recently, the invention of a hollow-core fiber to deliver the CO_2 laser (OmniGuide system, OmniGuide Inc., Cambridge, MA) (**Fig. 36.1**) has broadened the indications for this surgery. It has removed the line of site necessary for management of the tumor and has brought the laser into the field on a flexible fiber. This, in combination with angled endoscopes, microinstruments and high-definition optics, has allowed for continued expansion of the use of this TLM.

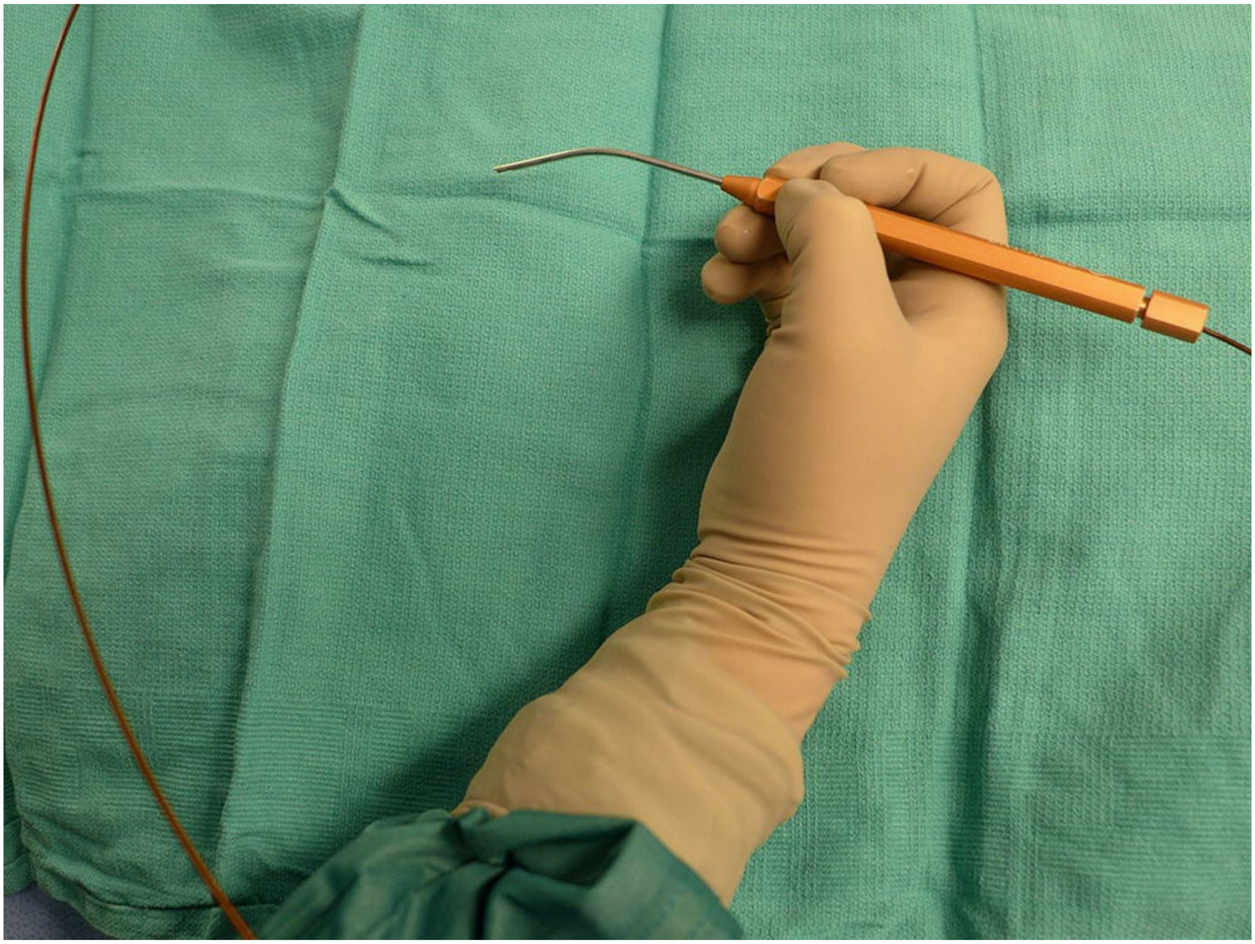

Figure 36.1. One of many interchangeable handpieces for the OmniGuide flexible CO_2 laser.

History of Robotics in Otolaryngology

In many ways, robotic surgery is the natural extension of endoscopic surgery. Although the endoscope has allowed our optical equipment to move into the field, it has also made distal control of instrumentation more challenging. Thus, the obvious target for surgical innovation as it relates to minimally invasive surgery is to explore the notion of improved distal control of instruments. This is one of the areas in which robotics excels.

The presence of robotics in surgery has been a relatively recent phenomenon. In fact, despite the presence of robotics in nonmedical industries for over 60 years, the first reported robotic surgical case was performed in 1985. The Puma 560 was used to accurately localize neurosurgical biopsies. The same device was then used to perform

transurethral biopsies of the prostate.[9] In 1992, the U.S. Food and Drug Administration (FDA) approved the first medical use of a robot. During the same time period, NASA and the Department of Defense became interested in the notion of remote battlefield surgery. Through DARPA, these agencies funded this technology. It was conceptualized that deploying a remote controllable (telepresence) robot into the front lines of battle would allow a wounded soldier to be stabilized during the "golden hour" of trauma. This robot would be controlled by surgeons in a safe zone, allowing them to perform surgery during this critical window for survival, but without putting the surgeon in harm's way. The funding for this project helped catalyze the creation of the first commercially available robotic systems, the AESOP (Computer Motion of Santa Barbara, CA) and the da Vinci (Intuitive Surgical, Sunnyvale, CA). Variations of these systems are the backbones for the robotic systems we use today.

In otolaryngology (OTO-HNS), the primary robot in use today is the da Vinci system. In some ways, the word "robot" is a misnomer, in that full control of the instruments still rests in the hands of the operating surgeon. However, what sets it apart from other surgical tools is that the surgeon is controlling the instruments remote from the patient's bedside. In its current form, the da Vinci robot consists primarily of two components. One is the surgeon console, where the operating surgeon sits. This consists of a stereoscopic (three-dimensional image) set of goggles, as well as controls for the robotic instruments (**Figs. 36.2 to 36.6**). The second component is the bedside patient cart, which consists of three separate instrument arms, with interchangeable instruments, and a camera arm all controlled by the operating surgeon. What makes these instruments different than most others is that they are designed with distally wristed function, so that they have the capacity to mimic or even exceed the natural range of motion of a human wrist. This gives the operating surgeon seven degrees of freedom with movement of the instruments. In combination with the stereoscopic view afforded by the dual optic rigid camera arm, these small wristed instruments are well suited for surgery around corners or in tight spaces.

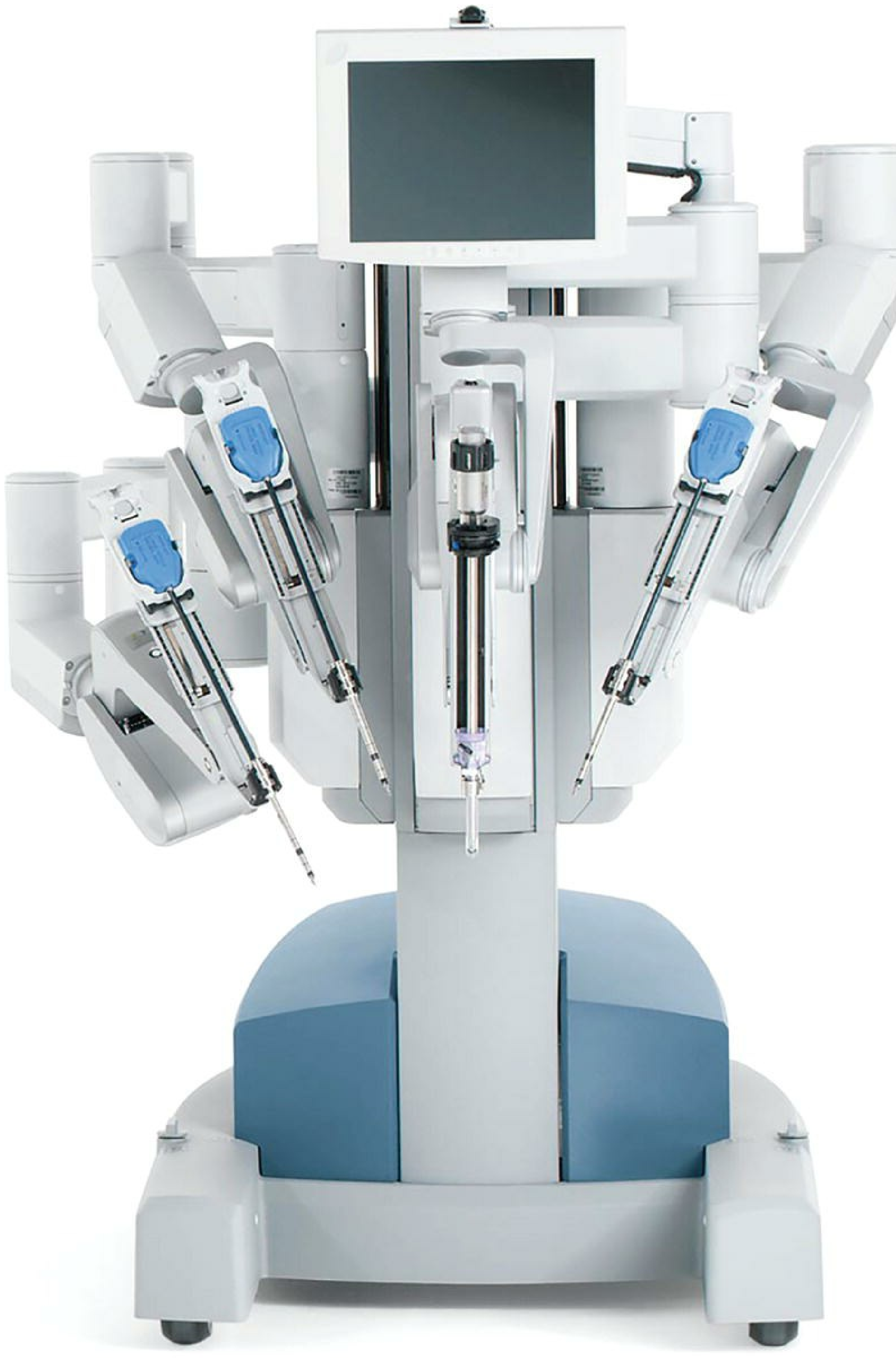

Figure 36.2. The Intuitive Surgical da Vinci bedside robotic console. Note the three instrument arms and the camera arm. (©2016 Intuitive Surgical, Inc.)

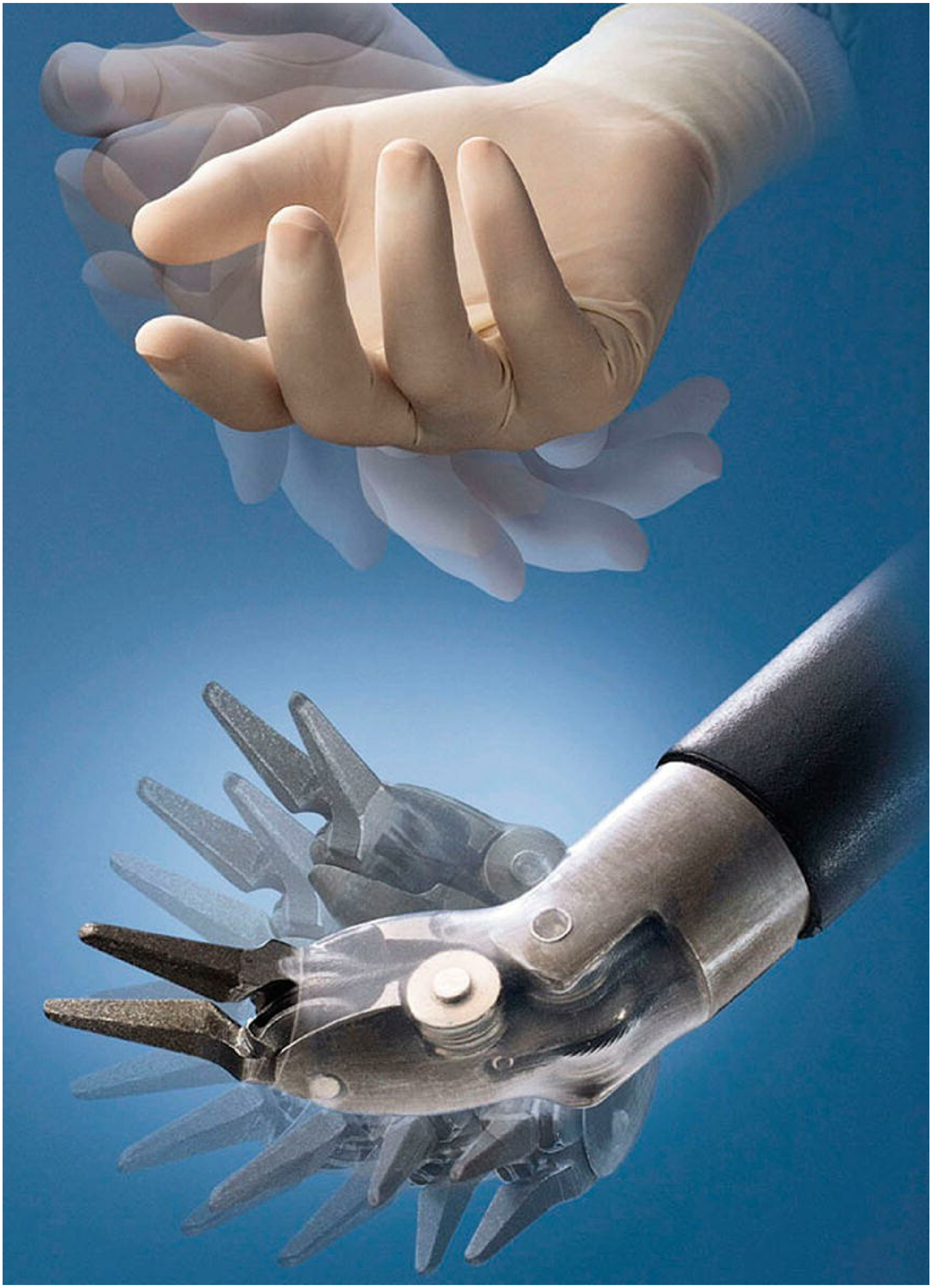

Figure 36.3. The end of the instrument arm on the da Vinci robot mimics the human wrist in creating seven degrees of freedom. (©2016 Intuitive Surgical, Inc.)

Figure 36.4. Close-up of the joystick-like controller used to move the robotic instruments. (©2016 Intuitive Surgical, Inc.)

Figure 36.5. Surgeon at the console, using the joystick-like controls. (©2016 Intuitive Surgical, Inc.)

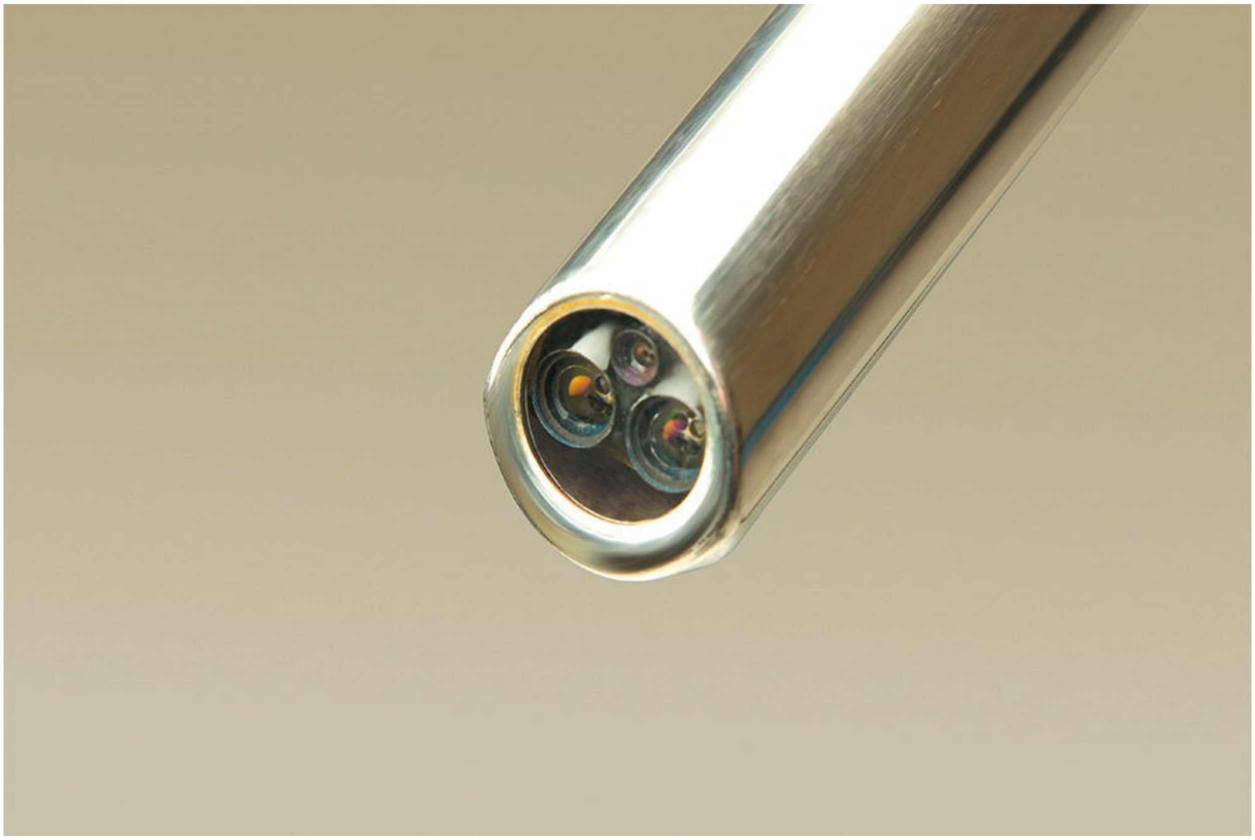

Figure 36.6. Close-up of the end of the camera arm, which houses two separate high-definition cameras and a light source.

The introduction of robotics to the field of OTO-HNS only occurred in the early 2000s. Initial reports described the use of the robot to help avoid neck incisions for surgery such as resection of a submandibular gland.[10,11] The first use of the robot in a live patient was for the removal of a vallecular cyst, published in 2005.[12] Within the next year, Drs. O'Malley and Hockstein described the first preclinical experiments that helped to establish transoral robotic surgery (TORS).[13] Building upon these original experiments, Drs. Hockstein, Weinstein, and O'Malley at the University of Pennsylvania developed preclinical models to demonstrate the feasibility, safety, and efficacy of TORS. This included application of the technology to cadaver, and live canine procedures, prior to performing human studies.[14–17]

Initial experiments surrounded the appropriate instrumentation for use with the robotic console. Most conventional laryngoscopes have a narrow inlet. This only allows for small, relatively parallel instruments to be inserted and used in the field. However, the robotic arms required broader access to

the field. This obstacle was overcome by the incorporation of several different retractors. Early use of the Dingman, Crow Davis, and FK-WO laryngoscope provided enough room for the arms of the robot to access the pharynx (**Figs. 36.7** and **36.8**).

Figure 36.7. Dr. Gregory Weinstein in an early case of TORS, placing a retractor into the patient’s mouth.

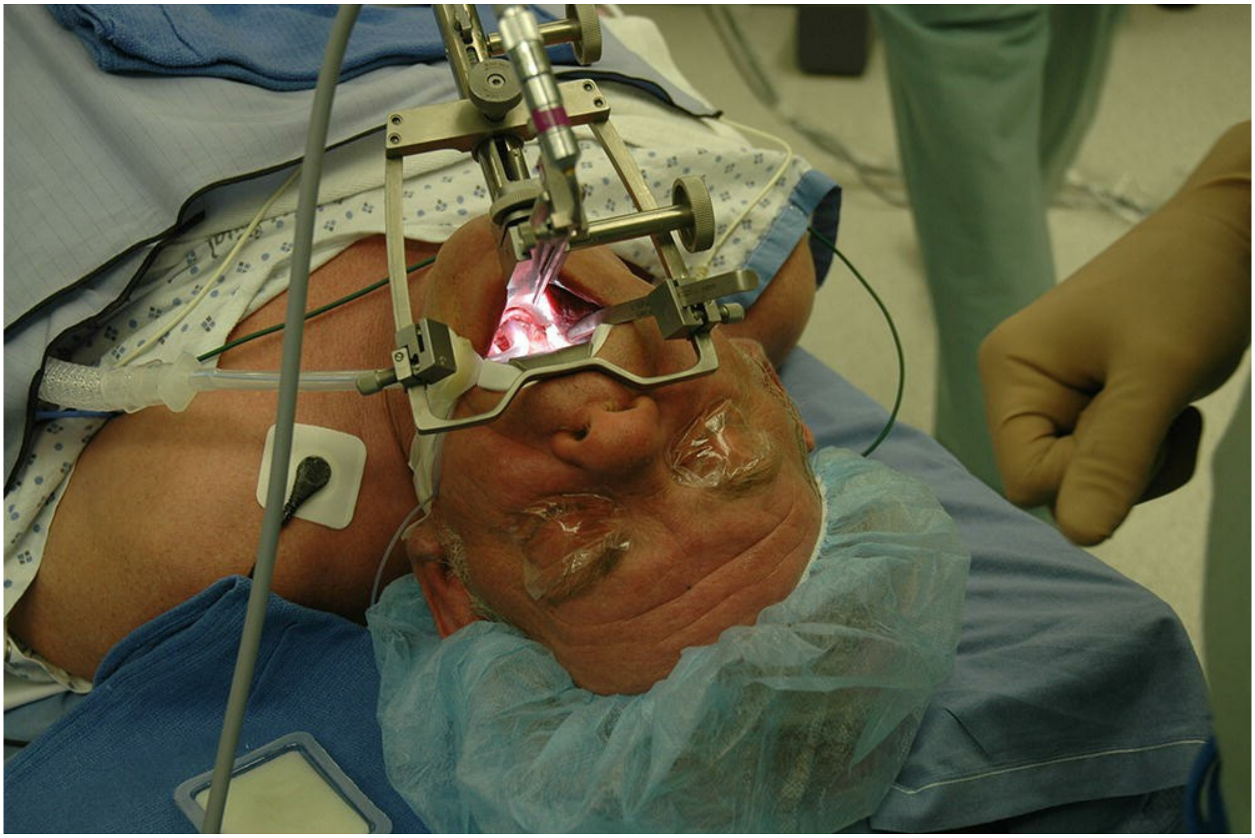

Figure 36.8. FK retractor in place, giving exposure of the surgical site and allowing adequate movement of the surgical arms.

After appropriate access to the surgical site was accomplished, creating a safe set of procedures with low-risk profile was the next priority. Additional studies were performed to look at these parameters. We concluded that transoral robotics surgery was safe and effective. This set the stage for human clinical trials.

Weinstein and O'Malley established a prospective human trial and conducted the first human experiments for TORS. The experiments included patients with various pathologies, including cancers of the oropharynx, larynx, and a variety or other benign and malignant conditions in the head and neck. These data,[16] pooled with the data from several other authors,[18] led to the approval from the FDA in December of 2009 of TORS for use in benign and select malignant lesions of the head and neck.

CURRENT INDICATIONS FOR

ENDOSCOPY AND ROBOTICS

Oropharynx

Endoscopy

Due to the somewhat restricted access to tumors of the oropharynx, open surgery to this area is particularly complex. This approach often involves a mandibulotomy for access, a tracheostomy to secure the airway, and often a feeding tube to allow for healing of the surgical site postoperatively (**Fig. 36.9**). In addition, just achieving adequate exposure can result in one or more cranial neuropathies. Fortunately, alternatives to the open approach began to show promise. Beginning in the 1970s, radiation began to play a role in the postoperative setting and then as primary therapy for cancer of the oropharynx. As the results began to demonstrate efficacy, many centers began to favor a radiation-based approach to these cancers. In many cases, a completely nonsurgical approach to this area was gaining acceptance. The combination of chemotherapy and radiation has now become one of the standard options for the management of cancer of the oropharynx. The oncologic outcomes are generally good, leading to 3-year overall survival rates between 23% and 88%.[19,20] However, posttreatment sequelae can be significant with gastrostomy tube dependence rates ranging from 0% to 26% in the same literature.

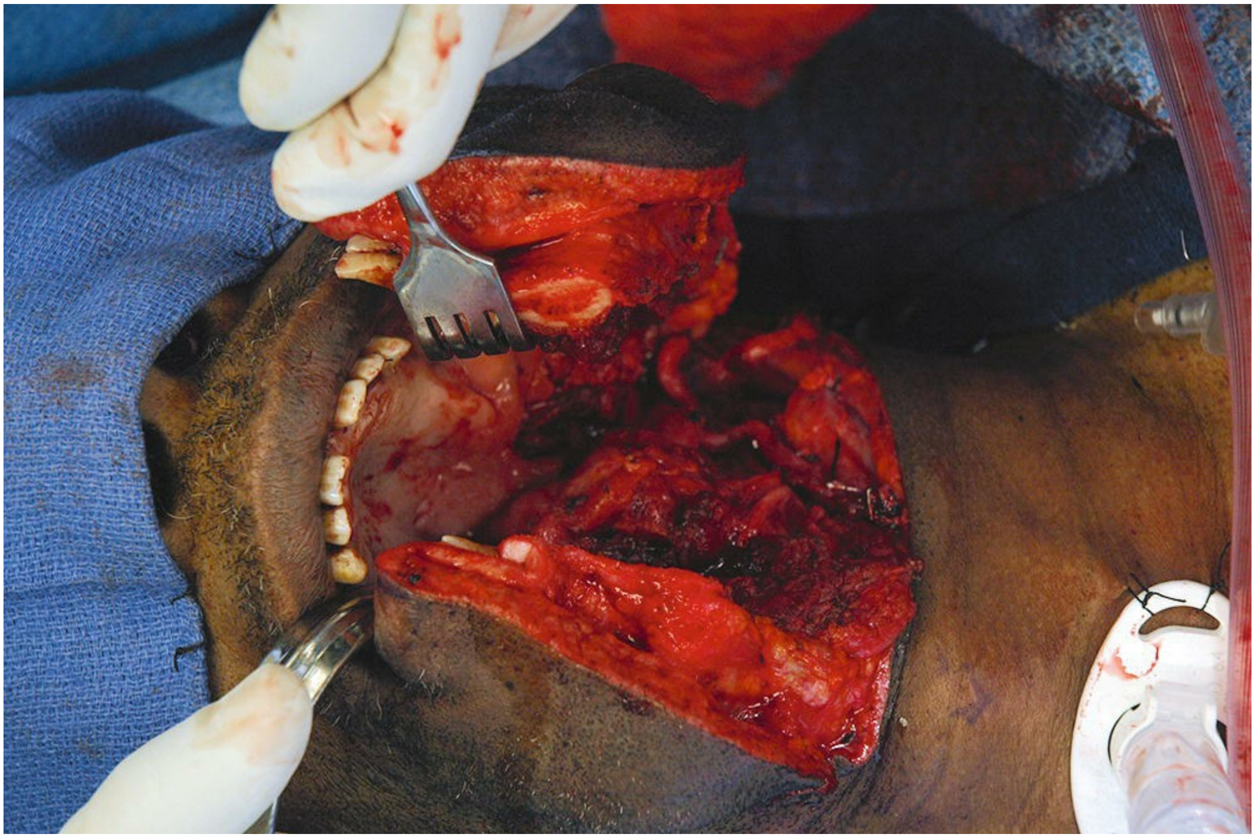

Figure 36.9. Traditional approach to tumors of the oropharynx. Note the mandibulotomy and tracheostomy.

The disease significantly increased in incidence over the same time period that the nonsurgical management of oropharyngeal cancer continued to gain acceptance. What was once an uncommon cancer primarily associated with smoking and drinking, largely affecting men in their 60s or older, has now become predominantly a virally induced (HPV) cancer, affecting many nonsmokers, often in their 40s and 50s. This change in the etiology of the cancer has been associated with an improved response to therapy and overall survival of patients with HPV positive tumors. Concurrent with our enhanced understanding of the biology and clinical behavior of HPV positive oropharyngeal cancers, the technology used to treat them has also evolved. The options for surgical management of primary cancer of the oropharynx have developed considerably and will be discussed below. In addition, even the management of the neck, once limited to a radical neck dissection, has now been shown to be amenable to more limited selective neck dissections.

At the same time that many centers were advocating a nonsurgical approach to cancers in the oropharynx, surgeons in Europe including

Professor Wolfgang Steiner are credited with expanding the nascent field of TLM.[7] This surgery is an alternative to primary radiation and at present is also an alternative to robotic surgery for the oropharynx. TLM, much like TORS, has benefitted from the evolution of optics and instrumentation and has the potential to give excellent outcomes without the need for open surgery. Steiner's approach involves the use of distending bivalve laryngoscopes. This allows the surgeon to apply tension to the cancer and resect using the CO_2 laser at the appropriate distance from the tumor. This approach often requires a "piece-meal" transection of the cancer in order to continuously evaluate the depth of the tumor and to obtain clear its margins. Although the adoption of this technique has been slow, it has resulted in excellent outcomes in repeated studies, from multiple institutions. Several studies have demonstrated an excellent overall survival for patients using this technique, with rates from 52% to 87%.[21–24]

Robotics

The anatomic site that has benefitted most from the use of robotics in the field of head and neck surgery is the oropharynx. Although some of the earliest robotics experiments were performed in the larynx and neck, the robotic technology appeared best suited for the management of cancer in the oropharynx.[25] The combination of improved visualization, four-handed management of the cancer, and relatively easy instrument access to the surgical site made this an obvious choice. Cancers in the tonsil and base of tongue are the primary targets for TORS (**Fig. 36.10**).

Figure 36.10. Early photo demonstrating the technique for surgical setup for TORS.

Prior to the creation of TORS, many of the patients with cancer of the oropharynx had limited surgical options. Open approaches are associated with significant morbidity and in the current era are often reserved for recurrent cancer after nonsurgical treatment. Although TLM has clearly demonstrated the feasibility of a nonopen approach to cancer of the oropharynx, the technical challenges of this approach have limited its acceptance.[26] This combination of feasibility and technical challenges of TLM paved the way to the introduction of TORS for management of cancer of the oropharynx. Several of the obstacles facing a surgeon with TLM are removed with TORS. Reduction of the need for line of sight, the ability to use four-handed technique, improved hemostasis, a wider field of view, and wristed distal dexterity instruments have all made the resection of tumors in this area less challenging (**Fig. 36.11**). Although still less than a decade since its inception, the early results are good. Several studies have reported 2- and 3-year overall survival results from 85% to 92% in selected patients.[27–29]

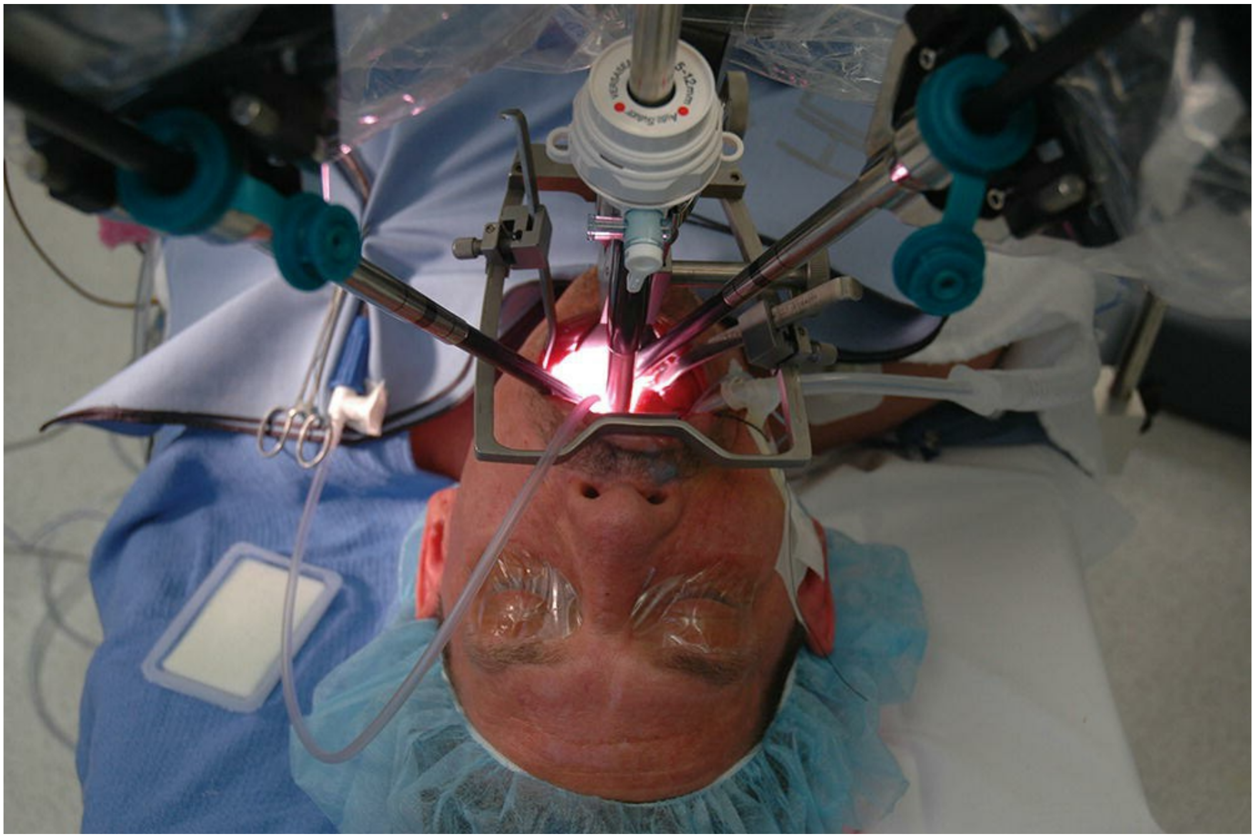

Figure 36.11. Surgical setup, demonstrating the position of the instrument arms and the camera arm.

TORS is performed using a variety of laryngeal and oropharyngeal retractors. Once adequate visualization of the cancer is obtained, the robotic arms are brought into place in the oral cavity. The primary surgeon sits at the console, and the assistant at the patient bedside, at the head of the patient (**Figs. 36.12** and **36.13**). This two-surgeon approach allows for excellent suctioning, retraction, and hemostasis, as four hands are in the field at once. Because this exposure generally allows for a view of the entire tumor, an "en-bloc" approach is often possible and favored.

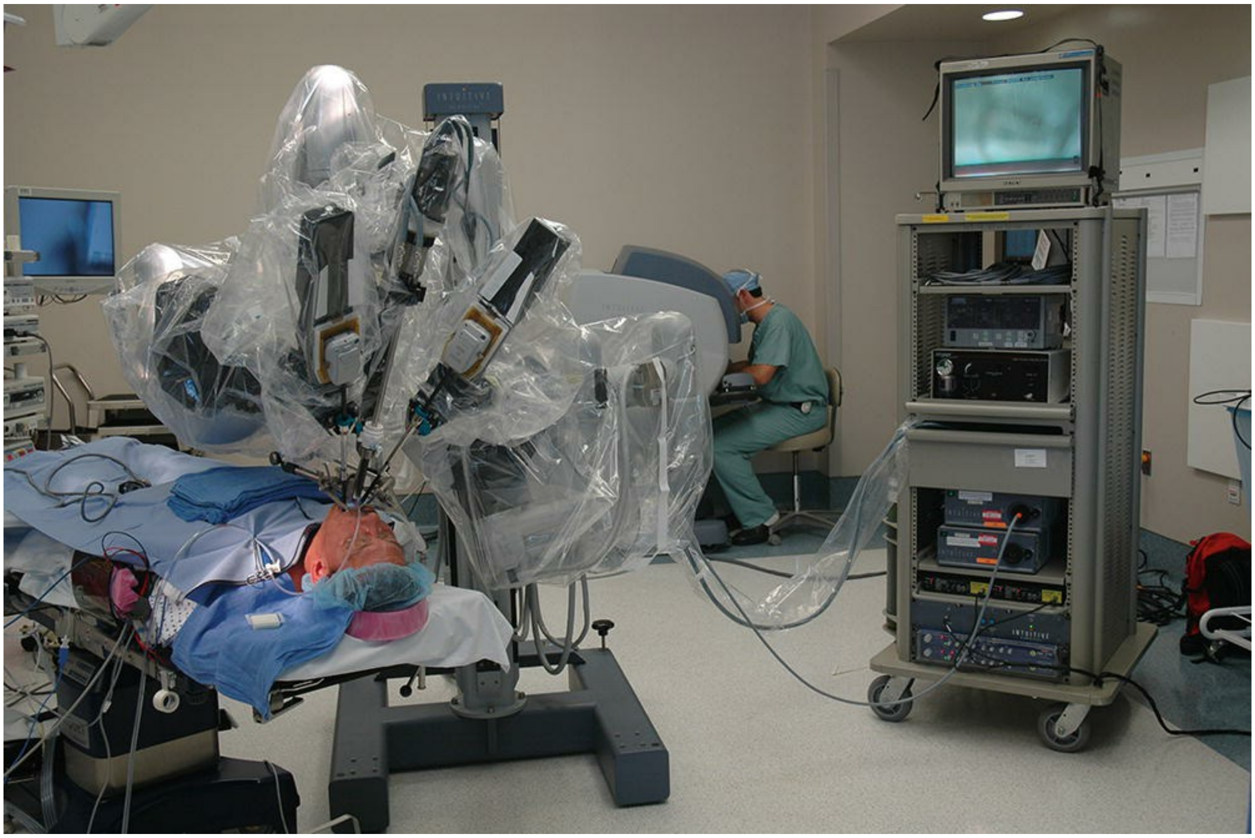

Figure 36.12. Setup of the room and the robotic instruments in an early surgical case. The bedside console, the vision cart, and the surgeon console are all visible.

Figure 36.13. Operating room setup for TORS.

Clear indications, tumor characteristics, and contraindications have now been set out for TORS. They include features listed in **Table 36.1**.[9]

Table 36.1 Indications and Contraindications for TORS

Indications
1. Adequate visualization of the tumor
2. Adequate exposure for resection
During staged laryngoscopy, the appropriate retractors may need to be inserted to determine if the tumor will be amenable to negative-margin resection with TORS techniques
Characteristics such as trismus, anterior positioned larynx, large tongue, or morbid obesity often make placement of the pharyngeal retractors impossible
Contraindications
Unresectability of involved neck nodes
Invasion of the mandible
Involvement of the base of the tongue requiring resection of >50% of the tongue base
Involvement of the pharyngeal wall requiring resection of >50% of the posterior pharyngeal wall
Radiographic confirmation of carotid artery involvement
Fixation of the tumor to the prevertebral fascia

The timing of management of the neck in patients undergoing TORS continues to evolve, as does the procedure itself. Initially, the neck dissection was routinely staged after the primary surgery, to reduce postoperative pharyngeal edema as well as to reduce the incidence of fistulization. Recently, many surgeons have begun to stage the neck component of the surgery before or at the same time as the resection of the primary. This may help to reduce the incidence of postoperative bleeding.

Larynx

Endoscopy

TLM (the history of which is described above) is an accepted standard in the treatment of well-selected patients with cancer of the larynx. There is an extensive literature demonstrating the safety, efficacy, and outcomes of this technique.[30–34] It is most often used in the management of previously untreated cancers, but results in the face of recurrence following radiation have also been quite good. Because good exposure is one of the keys to success in this surgery, a combination of closed or distending laryngoscopes is used to visualize the cancer.[31] The technique, especially for larger cancers, often involves a stepwise resection of the cancer by cutting through the cancer with the laser in order to create a three-dimensional map of the depth and extent of the cancer. Specific blocks of cancer are then removed until the entire cancer is resected with frozen section evaluation of the margins. The laryngoscopes are repositioned as necessary during surgery in order to optimize exposure.[35] TLM has been advocated for use in many early-staged glottis cancers, but has also been shown to be effective in the treatment of selected patients with more advanced, staged T3 and T4 cancers[36] (**Fig. 36.14**). In select cases, it may also be an option for treating recurrent cancers after surgery or radiation-based therapies.[37]

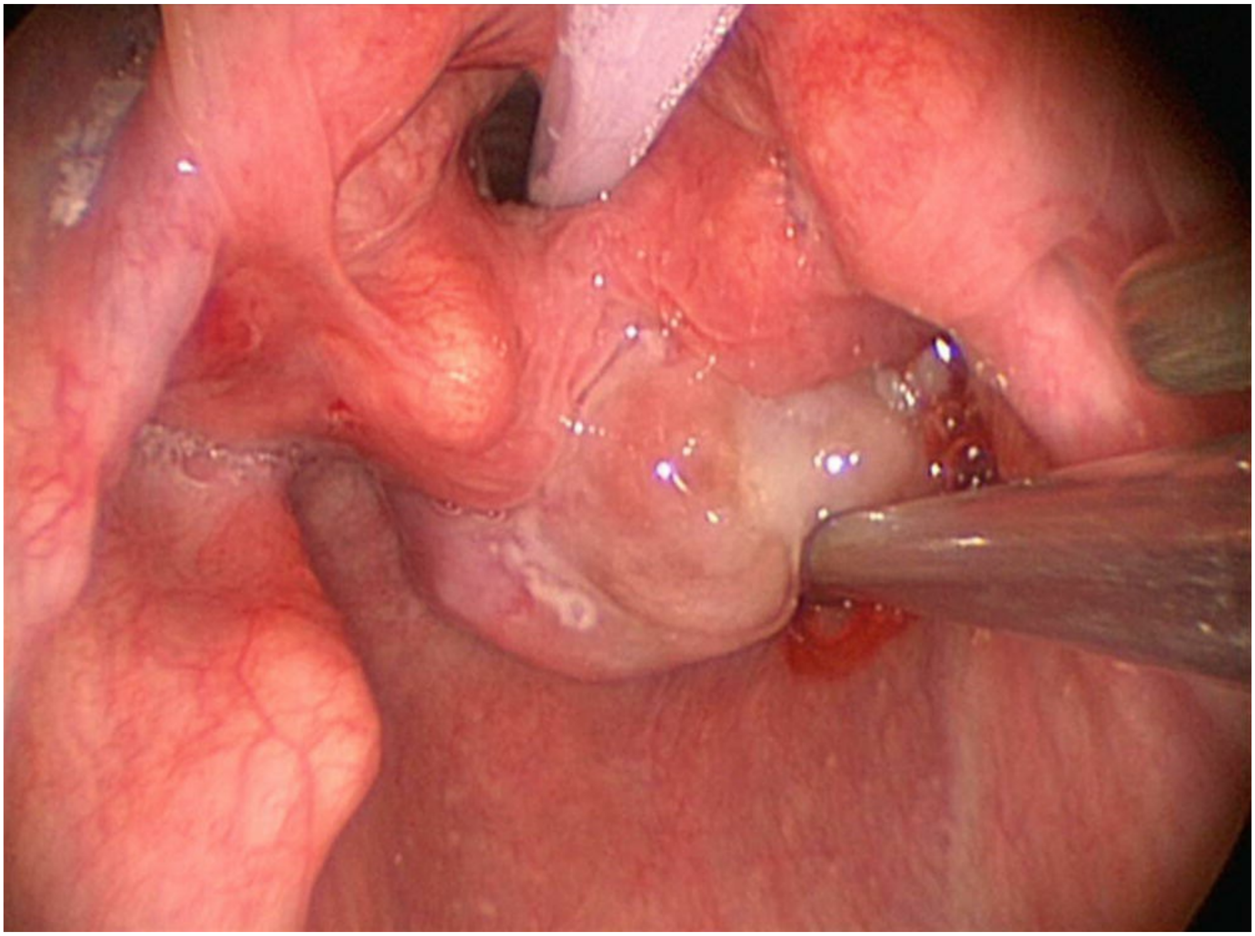

Figure 36.14. Excellent exposure can be achieved with the endoscopic approach to the larynx and hypopharynx, as is the case with this postcricoid tumor.

Robotics

Despite the early interest in the larynx as the main target of robotic surgery, it has not become the primary target of this new technology. Most current robotics series show fewer than 10% of cases to involve the larynx and even fewer of them to be cancers. This is due to a combination of factors. The da Vinci robot, as currently configured, lacks the microinstrumentation needed to operate on many regions of the larynx. Not only are the 5-mm instruments significantly larger than what is used in the nonrobotic approach but the instrument choices are still quite limited. Additionally, as the robotic instrument arms are placed further into the oral cavity and oropharynx, they begin to reach the limit of their practical utility. The range or motion and rate of "collisions" at the proximal end of the arms become an obstacle to safe

surgery at this depth.

Additional factors are also responsible for the small percentage of cases of laryngeal cancer treated robotically. Primarily, there are at least two excellent competing options for their management. One is nonsurgical therapy, which, for many primary laryngeal cancers, has been demonstrated to be a good choice.[38,39] The other alternative, for appropriate lesions, is TLM. Until the results of TORS are able to compete with either of these options, it will continue to play only a small role in the management of most laryngeal cancers.

Recently, several robotics companies have designed new systems to help address the difficulty in accessing the narrow confines and delicate anatomy of the larynx and other areas of the head and neck. These systems use special retractors and flexible snake-like cameras and smaller instruments to achieve this goal. As this technology continues to evolve, some of the obstacles that we currently face in the use of robotics will be eliminated, and greater applicability of this technology will inevitably occur.

The one area of the larynx, which may benefit from the use of TORS in its current form, is the supraglottis.[40,41] In the appropriate patient, supraglottic laryngectomy performed with the robot is safe, efficient, and perhaps easier than with TLM. Several larger series of TORS have included a small fraction of patients who have undergone supraglottic laryngectomy using the robot. Although most of the outcomes are early, the results so far are favorable.[29,42–44]

There have been several papers published on the results of small series of patients undergoing more extensive robotic surgery, including total laryngectomy.[45,46] This type of innovation will continue to push forward the frontier of surgical robotics, broadening the indications and helping to create better technology for the future of surgery.

Sinonasal and Skull Base

Sinonasal and Skull Base Endoscopy

Although the use of the endoscope for nonmalignant lesions of the sinonasal region dates back to the 1970s, it was less than two decades ago that the first report of management of a series of patients with sinonasal malignancies

(esthesioneuroblastoma) was reported by Casiano et al.[4] Since that time, endoscopy has played a significant and continuing role in the management of sinonasal and skull base malignancy. In fact, for many diseases, a completely endoscopic endonasal approach has become the standard approach.

As technology and techniques developed, surgeons grew more comfortable with managing more complex diseases through the endonasal corridor. Initial endoscopic assistance to open procedures led to eventual adoption of a completely endoscopic approach to many diseases. Early papers focused on the safety and feasibility of a completely endoscopic approach.[5,47,48] The management of CSF leaks and then of pituitary tumors were among the early procedures in which purely endoscopic approaches were adopted. These early experiences led the way to creating safe and effective techniques for both the resection and repair of the cranial base. In fact, one of the significant limiting factors in the endoscopic management of cranial base tumors was the challenge of separating the intracranial from the sinonasal space postoperatively.

Early attempts to resect tumors that involved large areas of the cranial base were fraught with high rates of CSF leak.[6,49–51] Many efforts have been made to solve this problem. Various grafting techniques, biologic materials, glues, and flaps have been designed. In 2004, Hadad et al.[52,53] described the first use of a vascularized, pedicled nasoseptal flap. This flap provided a wide, thick vascularized piece of tissue that could be used to help aid in the closure of the often large defects left by resection of the bone and dura of the anterior cranial base (**Fig. 36.15**). This solved, to a significant degree, the high rate of CSF leaks that were being seen as a result of resection of the cranial base. Once able to prevent the CSF leaks, more advanced procedures were designed to access tumors of the sinonasal spaces and cranial base. At the same time, the literature was beginning to show the equivalence and, in many cases, the superiority of endoscopic over open approaches in the treatment of tumors of the sinonasal and cranial base regions.[6,50,54–56]

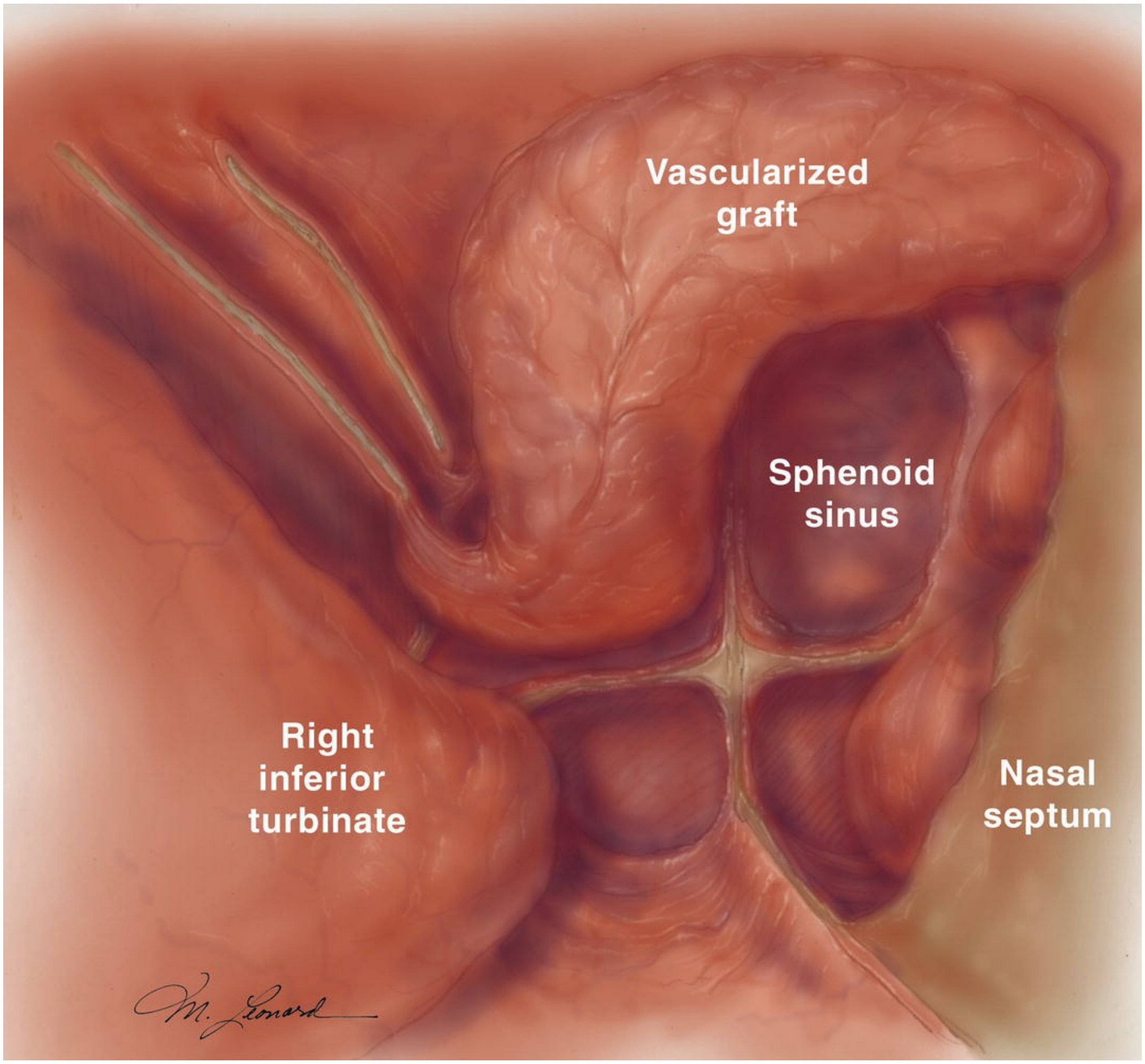

Figure 36.15. This represents an endonasal view, with depiction of an open sphenoid cavity, posterior septectomy, with a nasoseptal flap pedicled off of the right posterior septal artery and draped superiorly over an anterior cranial base defect.

At present, the entire sinonasal cavity and ventral skull base are appropriate targets of an EEA. Descriptions of approaches along the entire skull base along both the sagittal and coronal plane have been made. Each space along the ventral skull base has a separate set of parameters, which will guide the surgeon in the approach. In each approach, management of the instruments and the endoscope are key in helping to create a safe corridor to the region of concern[57] (**Fig. 36.16**).

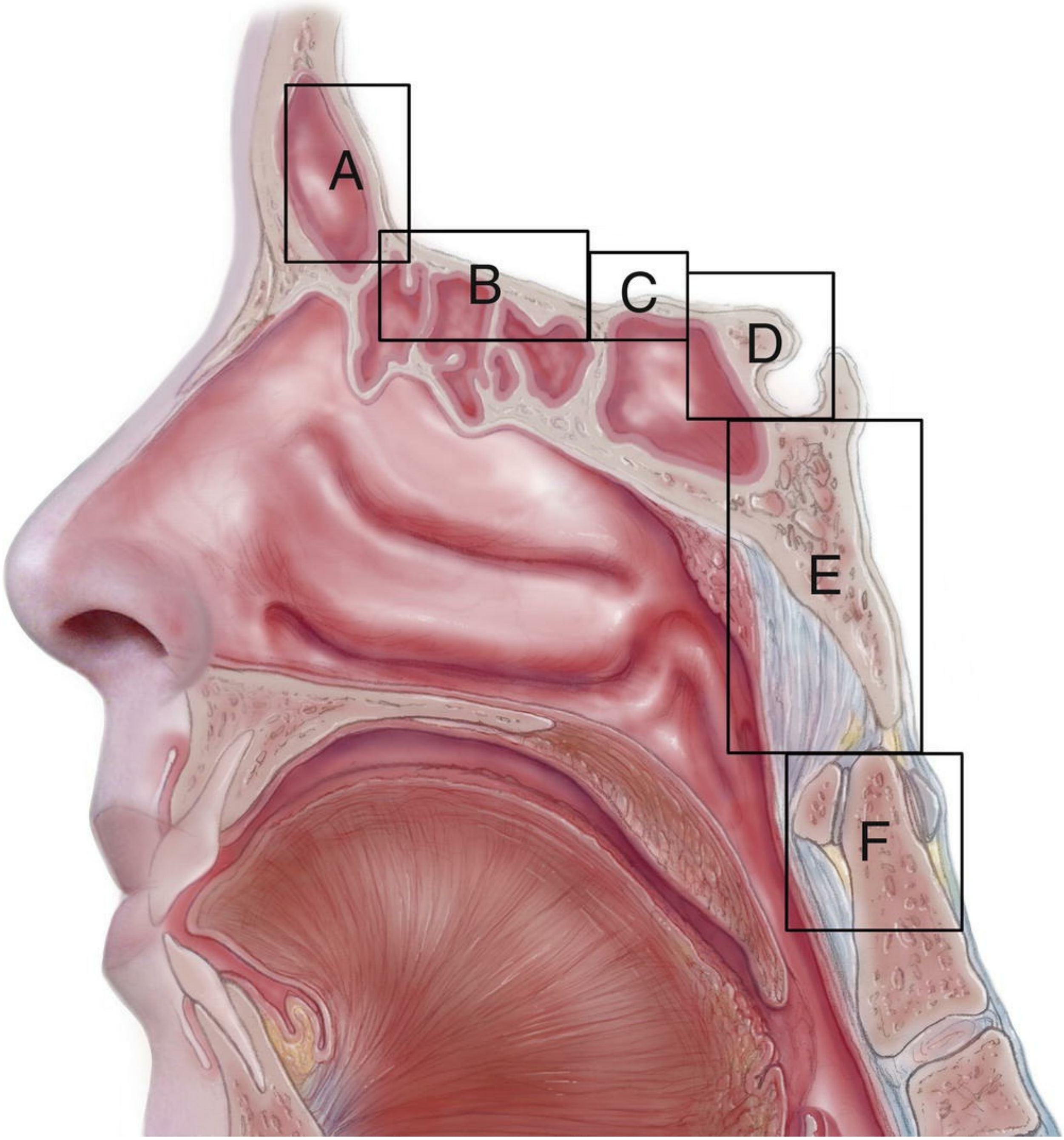

Figure 36.16. The multiple corridors accessible via a transnasal approach to the skull base. *A*, transfrontal; *B*, transcribriform; *C*, transplanum/transtuburculum; *D*, transsellar; *E*, transclival; *F*, transodontoid.

Having the technical capacity to approach tumors along the entire ventral cranial base is not the equivalent to being able to safely resect all tumors along this corridor. There are still several contraindications to EEA management of tumors of the cranial base. They are included in **Table**

36.2[55]: Of course, as instrumentation and technology evolve, these contraindications will continue to change.

Table 36.2 Contraindications for Endoscopic Endonasal Resection of Cranial Base Tumors
Involvement of the dura beyond the midorbital roof
Gross intraorbital extension
Involvement of the anterior table or far lateral recess of the frontal sinus
Extension into the facial soft tissues
Relative contraindications include Gross brain involvement Extension to the lateral wall of the maxillary sinus Extension to the lateral infratemporal fossa

An important aspect in the evolution of the endoscope as a tool in the management of sinonasal and skull base tumors is the evolution of the equipment and instrumentation used for these procedures (**Fig. 36.17**). In comparison to the original endoscopes used to perform early sinus endoscopy, significant progress has occurred. Not only has the optical clarity of the image been transformed but many other components of the visual experience have been augmented. Angled telescopes have allowed a modified view, around corners, and out of the direct line of site. High-definition cameras have created a clearer and more magnified picture of the surgical field. Systems to manage debris or blood on the end of the endoscope have made it possible to keep the endoscope in the field, without the need to disrupt the surgery. Recently, stereoscopic endoscopes have allowed surgeons to eliminate the distortion and reduced visual input that occur with use of a two-dimensional endoscope (**Fig. 36.18**).

Figure 36.17. Some of the equipment routinely used during endoscopy for skull base surgery includes a high-definition camera, surgical navigation, and irrigation sheath for the endoscope.


ALM

Figure 36.18. Surgeons performing endoscopic three-dimensional endonasal surgery.

Surgical navigation has also significantly affected the advancement of techniques in the sinonasal region. The bony anatomy of the cranial base is the perfect target for accurate anatomic navigation. It is possible to fuse CT and MRI images, in some cases being done in real time, in order to more safely and confidently navigate the bony and even soft tissue anatomy in this region (**Fig. 36.19**).

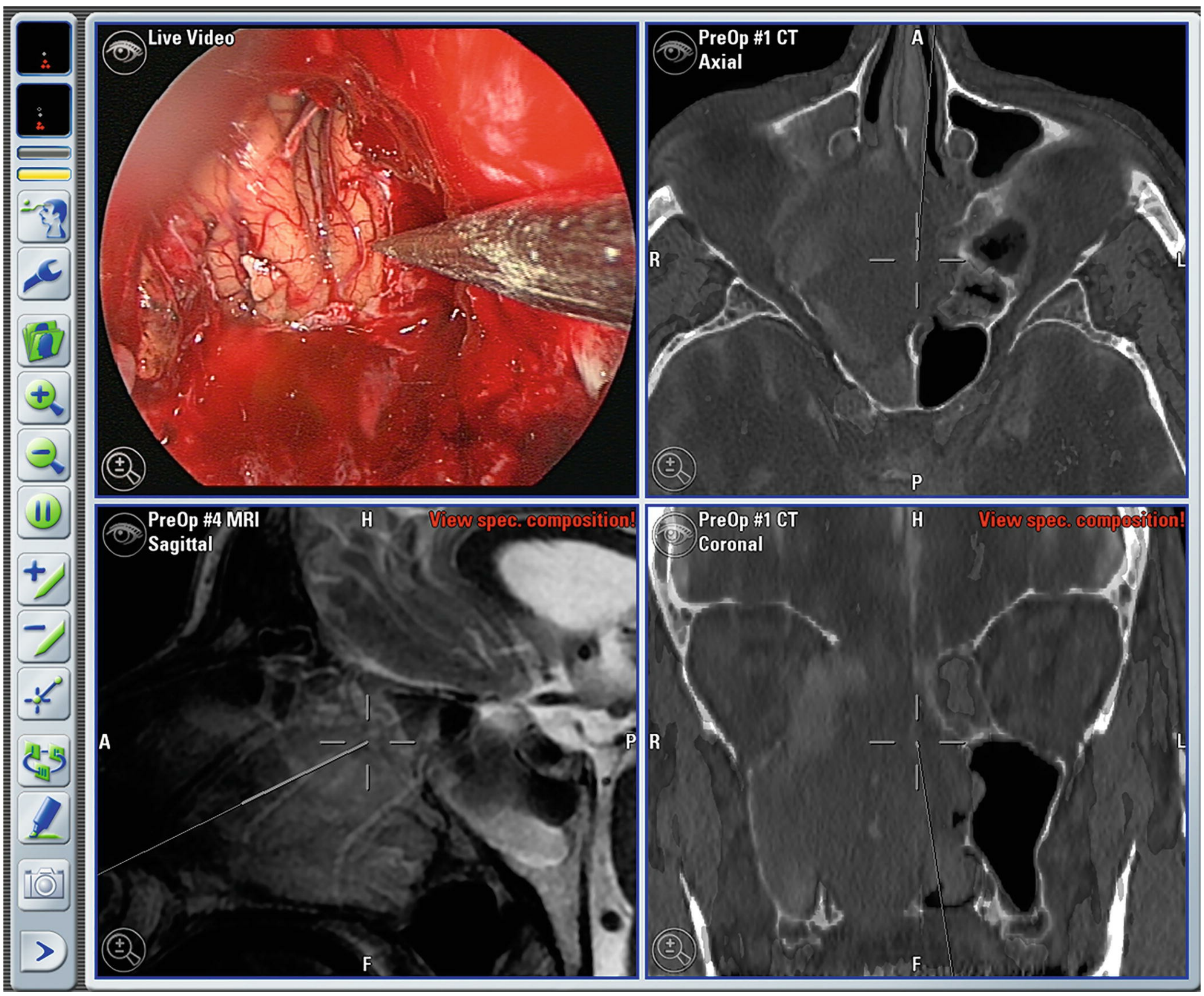

Figure 36.19. Four-panel view demonstrating the endoscopic view as well as fused MRI/CT views of the patient anatomy.

Instrumentation, including the microdebrider and the endoscopic drill,

has allowed the operating surgeon to effectively and safely manage both soft tissue and bony anatomy along the base of the skull. Newer instrumentation, including ultrasonic aspirators (**Fig. 36.20**) and tissue coblators, promises to deliver more precise tissue management to this area. The endoscopic ultrasound probe provides an additional level of assurance in the management of tumor abutting critical vascular structures including the carotid artery.

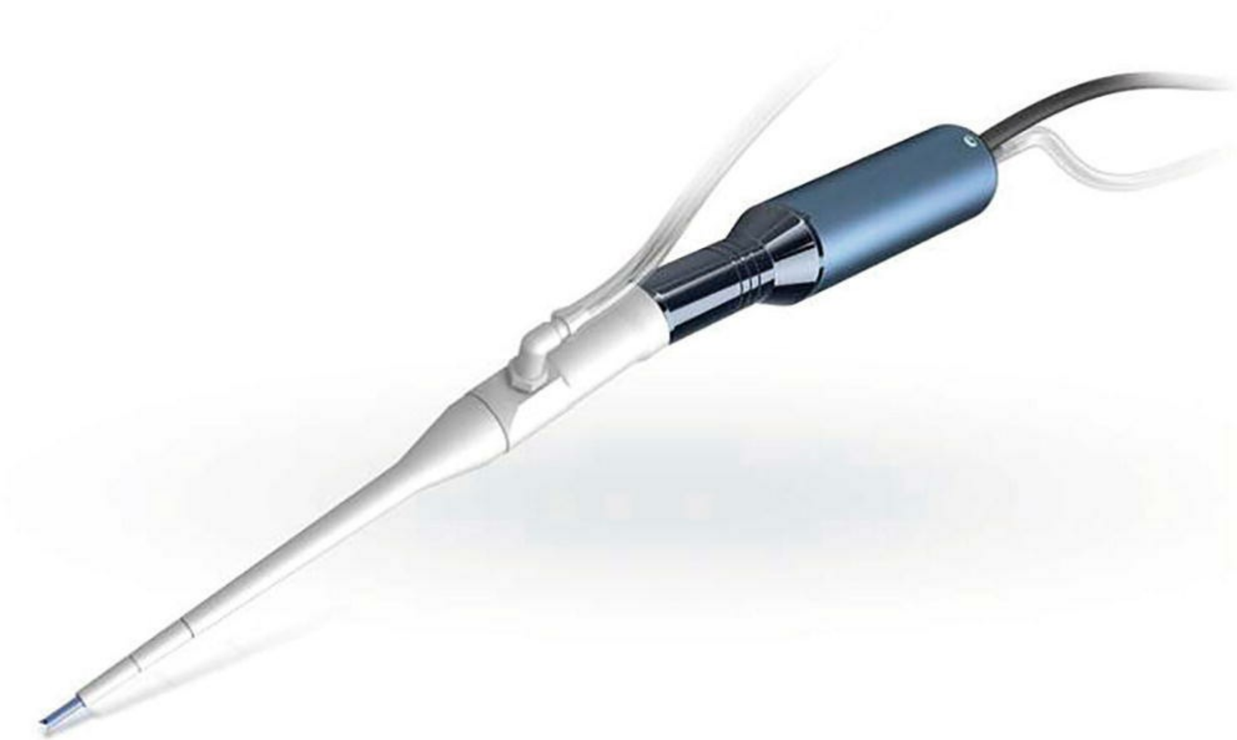

Figure 36.20. An endoscopic ultrasonic aspirator, the Stryker Sonopet.

Both synthetic and biologic products play significant roles in the advancement of endoscopy for lesions in the skull base. Hemostatic agents, dural and bony replacements, and tissue adhesives are three of the categories that have had the most significant impact.

Sinonasal and Skull Base Robotics

Robotic surgery for lesions of the anterior cranial base is still in its infancy. Several papers have been published describing the approach[58,59] with possible applications of this technology, but practically speaking, the instrumentation and setup of the currently available robotic system do not allow for a safe transnasal approach to this region. As soon as the

instrumentation and console can be designed to meet these parameters, it is nearly certain that transnasal robotic access to the anterior cranial base will become a reality.

Other parts of the cranial base, and other corridors, are now being explored by some surgeons as alternatives to open or endoscopic surgeries. Specifically, access to the parapharyngeal space has now been well described, and this route is being used in select cases of tumors in this region[60,61] (**Fig. 36.21**). The most common approach is transoral, with a lateral dissection involving a portion of the soft palate and lateral oropharyngeal wall. The most common indication is for prestyloid tumors, including salivary gland, neurogenic, and vascular tumors.[62] Potential advantages to this approach include excellent visualization compared to the transcervical open approach, the lack of an external incision, and reduction of first-bite syndrome. Much like conventional TORS, the addition of the robot to the approach to the parapharyngeal space adds the ability to place four hands into the surgical field (two of them being the robotic arms), to achieve excellent magnified visualization and to use angled endoscopes and instrumentation to access regions than cannot be accessed via nonrobotic approaches (**Fig. 36.22**).

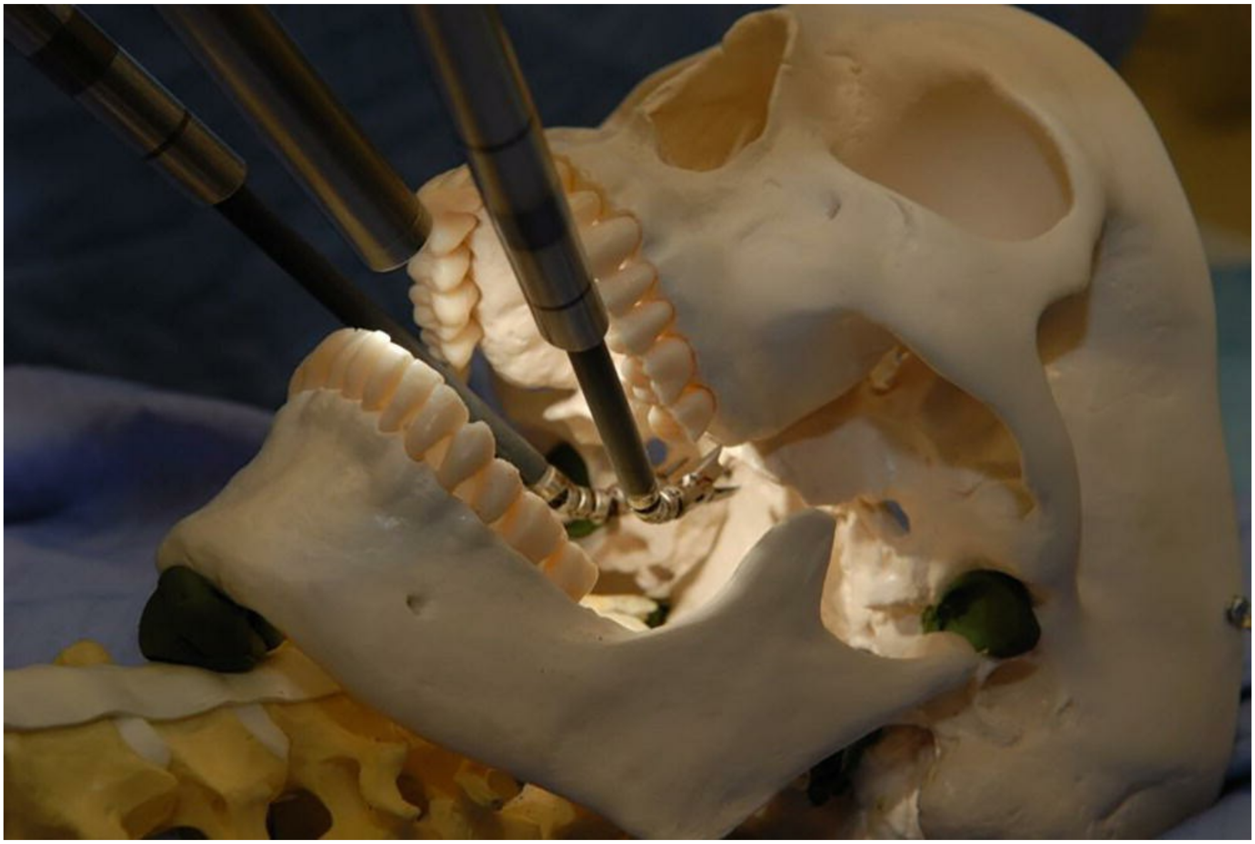

Figure 36.21. Conceptual approach to the base of the skull via the oral cavity. Note the wristed instrumentation.

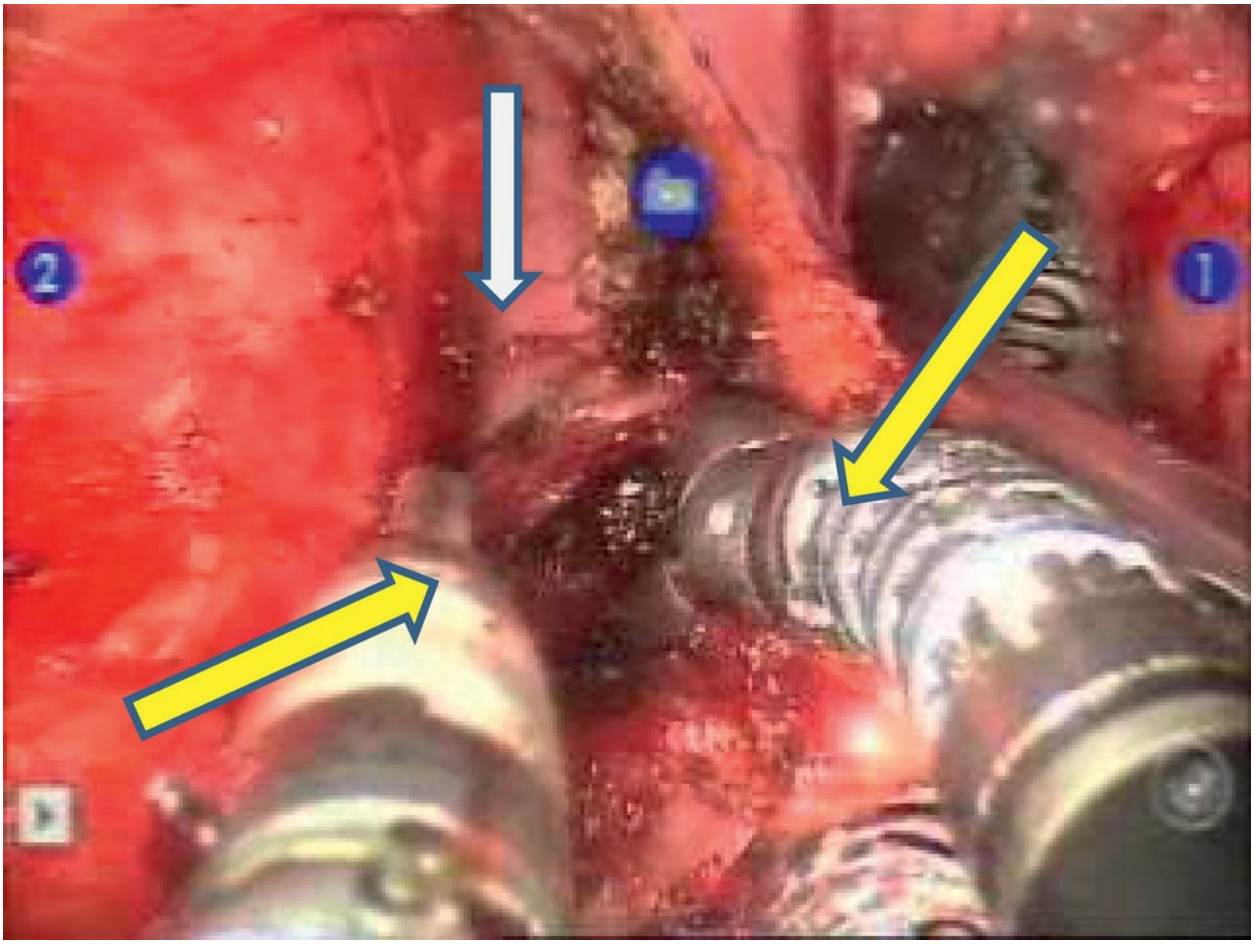

Figure 36.22. Transoral resection of a right parapharyngeal space tumor. *Yellow arrows* show robot Maryland forceps on right and Bovie dissector on left. A dissection is being performed in the parapharyngeal space at the junction of the pleomorphic adenoma tumor capsule and the constrictor musculature (*white arrow*).

Additionally, the transoral route has created robotic access to several other parts of the skull base, including the odontoid, craniocervical junction, infratemporal fossa, and[58,63–65] atlantoaxial spine (**Fig. 36.23**). As the technology and instrumentation evolve, these corridors and the procedures that can be performed through them will continue to expand (**Fig. 36.24**).

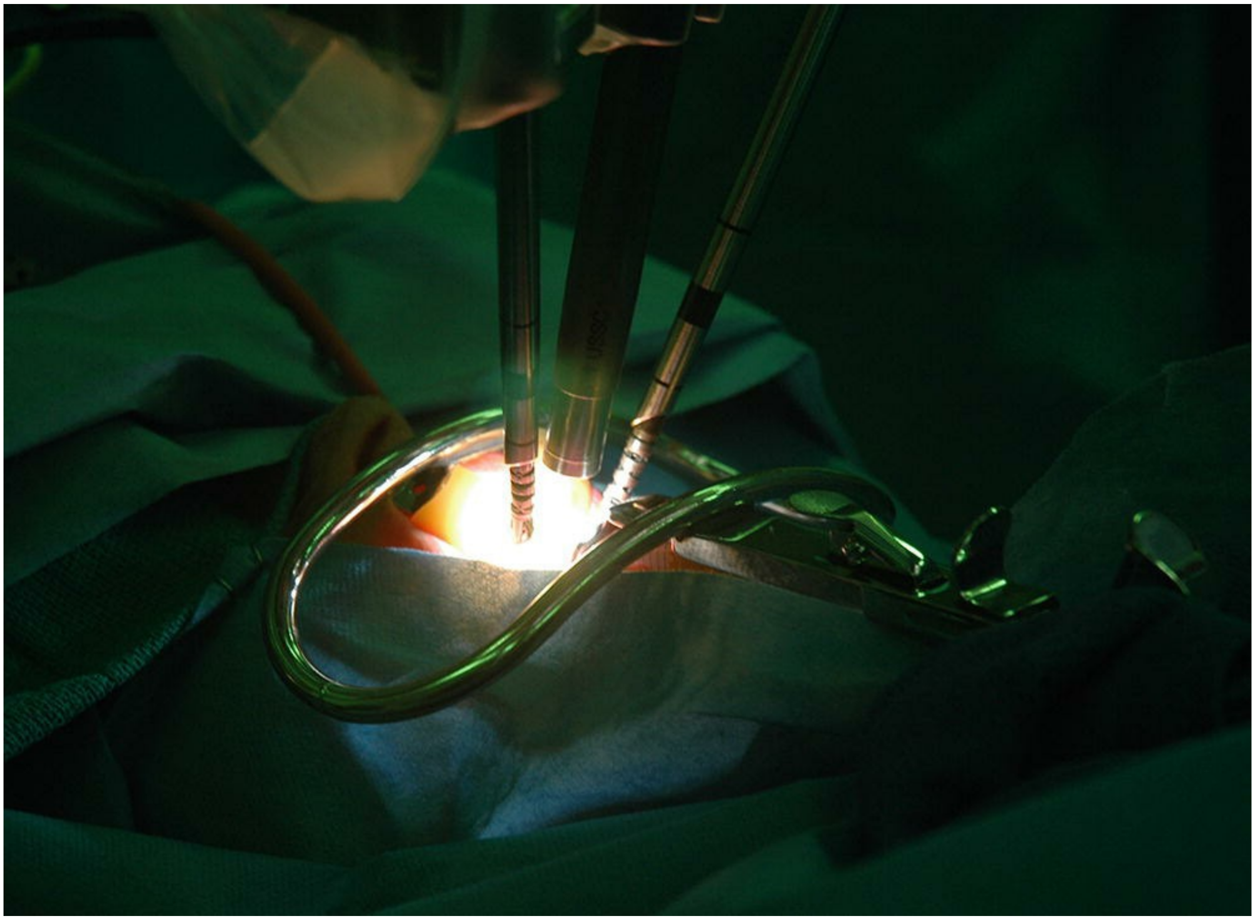

Figure 36.23. Robot docked for approach to the atlantoaxial spine. Note the instruments and camera are oriented toward the cephalad direction, unlike traditional TORS.

Figure 36.24. Early cadaver work demonstrating approach to the odontoid

via the oral cavity.

Thyroid and Neck

Endoscopy

In 1996, Gagner described the first report of an endoscopic approach to the parathyroid.[66] This was followed closely by Hüscher, who described a video-assisted hemithyroidectomy.[67] These early studies led the way to a concept of further reducing the size of the access corridor to the anterior neck. One of the driving forces behind this minimal access surgery is patient preference. Especially for young, otherwise healthy patients, continued attempts to minimize or hide the anterior neck incision are appealing. The first series of patients treated with minimally invasive video-assisted thyroidectomy (MIVAT) was reported by Miccoli et al.[68] in 1999. One of the original goals of this surgery was to perform safely a "diagnostic" surgery on patients with follicular nodules of the thyroid. The surgery was performed through a 15-mm incision, and the combination of partial delivery of the thyroid and partial endoscopic techniques allowed for safe removal of the gland. Since that time, there has been significant expansion of the indications and techniques for this procedure. Although the main indication for this procedure remains diagnostic for follicular lesions of the thyroid, other indications, including the management of low-risk differentiated thyroid cancer (DTC) and small-volume benign disease, have been validated as a safe alternative to more open approaches.[69,70] Most commonly, the patients undergoing this approach are younger and more likely to be female than those who undergo an open approach to the thyroid.[71–73] This approach has become a standard option in many centers (**Figs. 36.25** and **36.26**).

Figure 36.25. OR setup for minimally invasive video-assisted thyroidectomy (MIVAT).

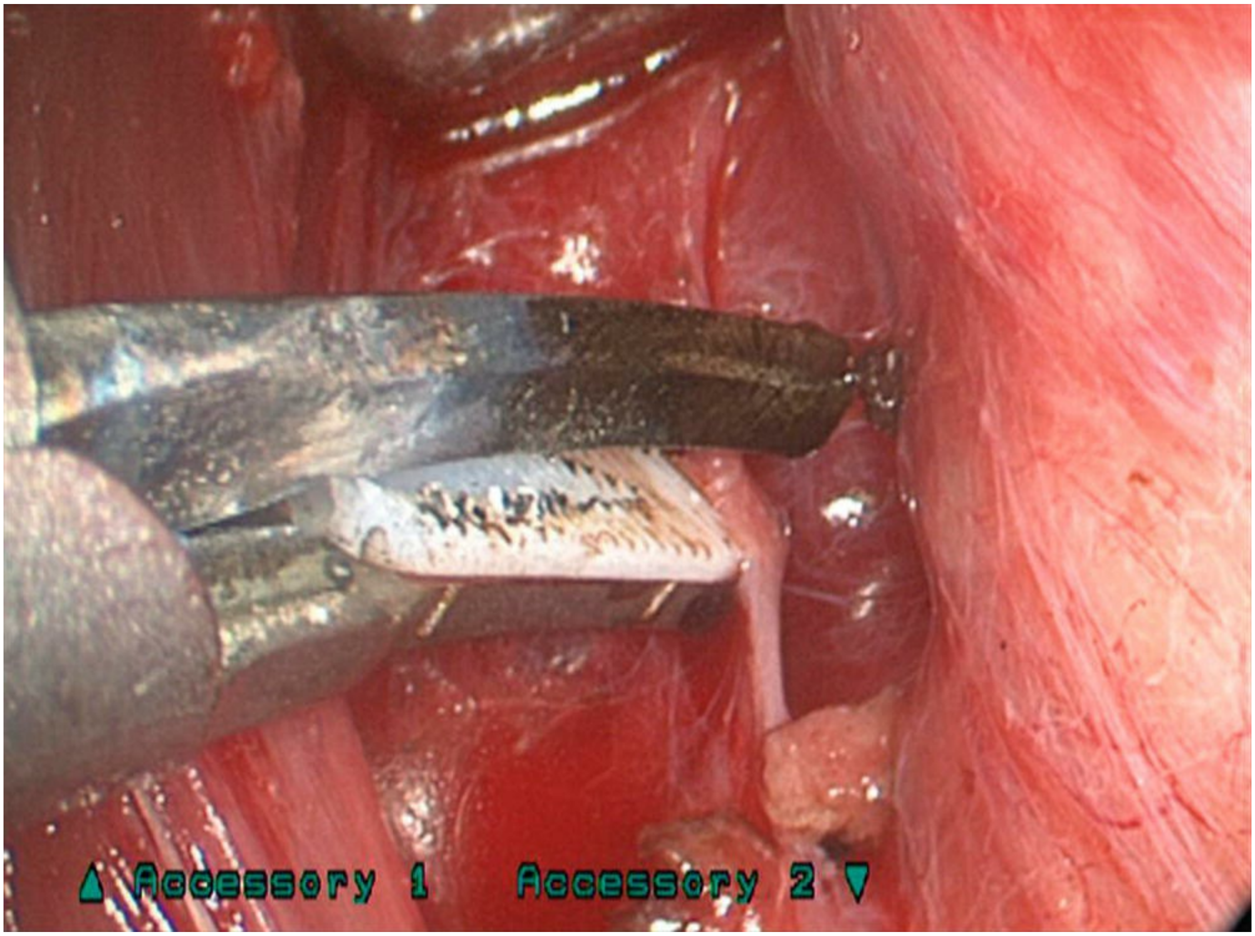

Figure 36.26. Close-up of the endoscopic view of the right superior pole of the thyroid, in preparation for ligating the vessels in this region.

Robotics

The endoscopic approach to the thyroid led the way to the application of robotic technology to this region. In 2006, Yoon et al.[74] described a gasless endoscopic approach to the thyroid via a transaxillary route. This approach completely eliminated the need for an incision in the neck. However, the endoscopic instrumentation made the surgery very challenging. In theory, some of the limitations of endoscopy, like the lack of stereoscopic view and the difficulty in manipulating nonwristed endoscopic instrumentation, could be overcome with robotic technology. In 2005, the robotic technique was first applied to the thyroid by Lobe et al.[75] The technique was then quickly brought into clinical practice by Kang, Chung et al. in South Korea, who in 2009 published their first experience with over 300 patients.[76] The technique involves making an incision in the axilla and then creating a working space

through this incision (**Figs. 36.27** and **36.28**). Retractors are placed into this space to allow dissection superficial to the pectoralis muscle. The robotic instruments are then introduced through this working space and used to visualize and dissect the thyroid via a lateral approach, retracting the strap muscles both above and below this field (**Fig. 36.29**). Once the thyroid has been resected, the incision in the axilla is closed, often with the placement of a drain.[9,77] Results from these surgeries are encouraging, and several studies have demonstrated both the safety and efficacy of this approach.[78–81] The cosmetic outcome is excellent, as the patient has a scar hidden in the axilla. There is no neck incision. However, due to the expense, added complexity, and the need for a relatively low-BMI patient, the surgery continues to fill only a small niche in its application to thyroid surgery in the United States.[82,83]

Figure 36.27. Patient positioning for transaxillary thyroid surgery. The patient's arm is extended and supported over the head.

Figure 36.28. Patient positioning for a left transaxillary thyroid surgery. The patient's arm is extended and supported over the head.

Figure 36.29. Operating room setup for transaxillary thyroid surgery. Note the angle of the robotic arms, docked in place to access the thyroid via the axilla.

Despite the lack of significant volume of transaxillary thyroidectomy being performed in the United States, the axilla as a corridor to the neck continues to have appeal. The transaxillary approach to the thyroid has paved the way for continued expansion of this corridor as an access route to the neck. Several authors have recently published an approach to the lateral cervical lymph nodes via this route, for the management of metastasis to the lateral neck.[84–86] Additionally, the concept of remote-access surgery to the thyroid gland has now been expanded to include a variety of different entry points. Terris et al.[87,88] described an alternate approach to the thyroid through a facelift incision, which may eliminate or reduce some of the difficulties encountered via a transaxillary approach (**Figs. 36.30** and **36.31**). As with early experience in the nasal and oral corridors, continued development of techniques and instrumentation will surely lead to further expansion of these techniques over time.

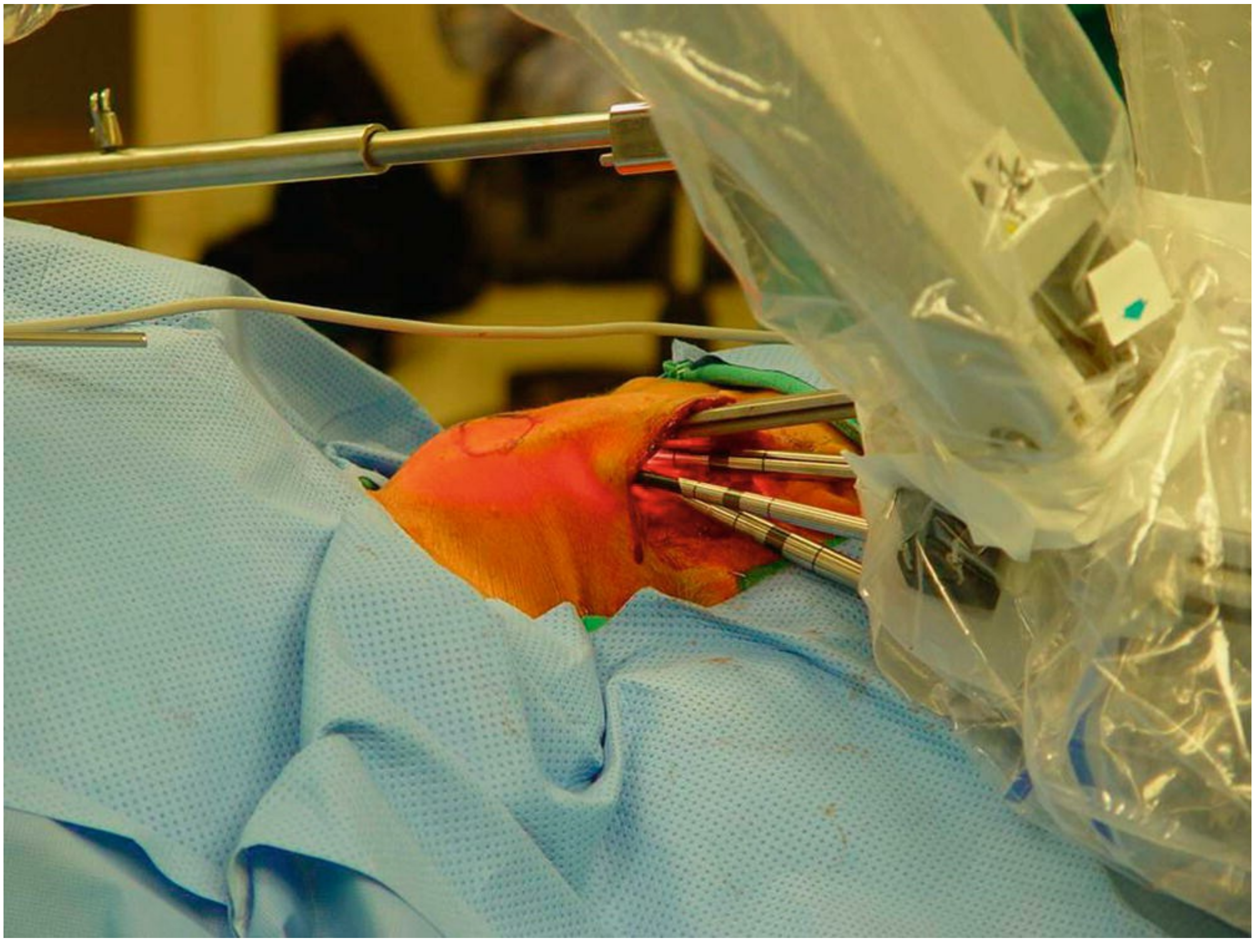

Figure 36.30. Robotic arms docked for a left-sided facelift-approach thyroidectomy. (Photo courtesy of David J. Terris, MD.)

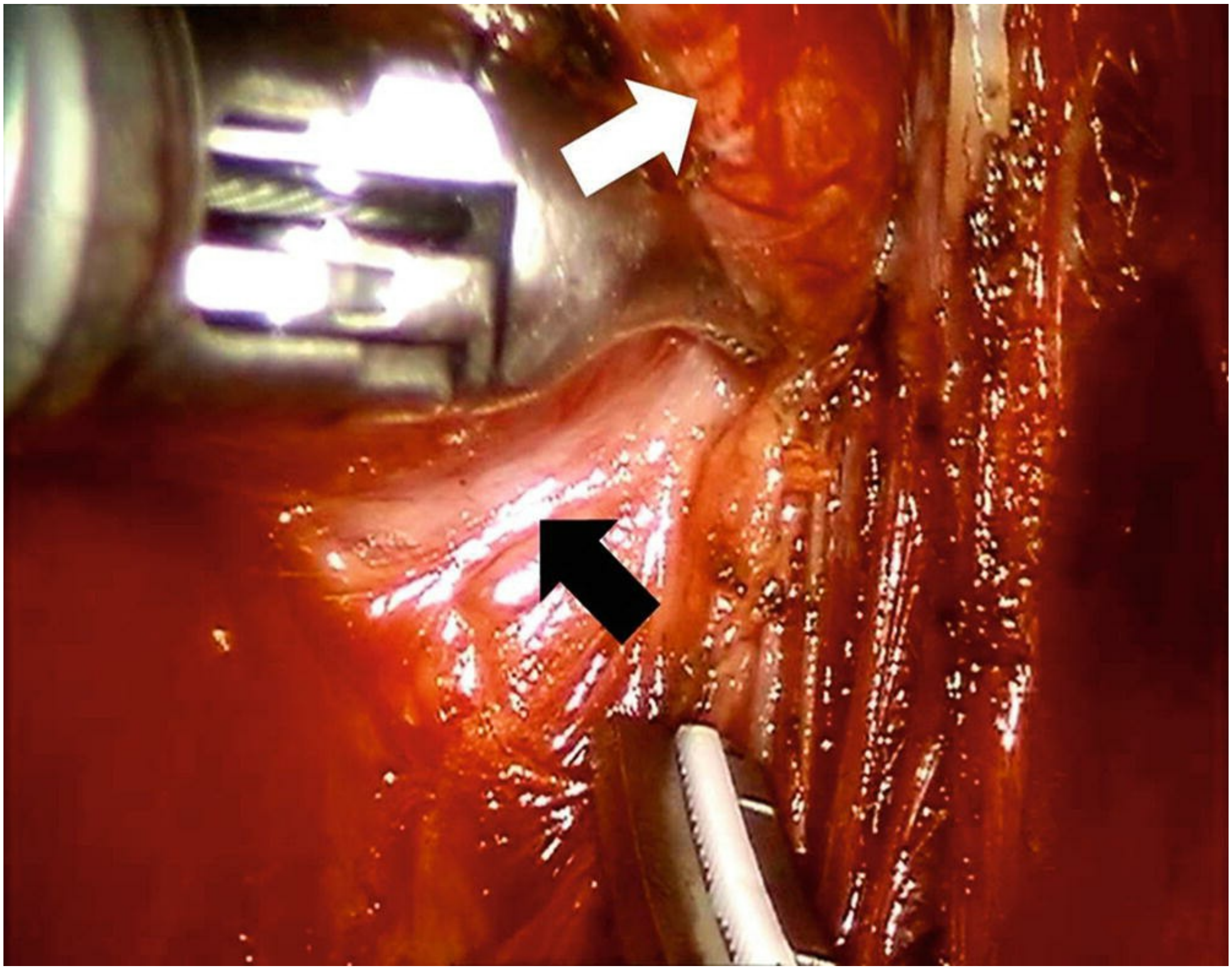

Figure 36.31. Robotic view of left thyroidectomy via a facelift incision. *Black arrow*, Recurrent laryngeal nerve. *White arrow*, Retracted thyroid lobe. (Photo courtesy of David J. Terris, MD.)

THE FUTURE

The technology and ingenuity in the fields of surgical endoscopy and robotics continue to change at a rapid pace. Even as this chapter is being written, several new technologies are on the horizon, including flexible robots, haptic feedback, and navigation-based robotic protocols. As the ability to scale this technology grows, as the costs come down, and as the indications expand, endoscopic and robotic technology will become increasingly useful in the world of surgery. It is likely that these fields will continue to play a greater role in the management of surgical diseases of the head and neck as we move into the future.

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37 Hemangiomas and Vascular Malformations of the Head and Neck

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INTRODUCTION

Hemangiomas and vascular malformations (VMs) are not cancers, but they occur frequently in the head and neck region and commonly present to the head and neck surgeon. These can be very destructive and even life threatening. The head and neck surgeon needs to know how to identify and manage these uncommon but complex benign vascular lesions. Furthermore, there is increasing evidence that many vascular malformations exhibit behavior similar to low-grade malignancies.

The treatment of vascular anomalies should be performed by an experienced team of specialists, consisting of surgeons, diagnostic radiologists, interventional radiologists, dermatologists, pediatricians, medical oncologists, and other specialties. Because of the psychological impact on these patients, it is important to understand and address this issue as well. Vascular anomalies may cause aesthetic complications, functional disorders, physical disabilities, and pain. These patients can become quite withdrawn and depressed, and these aspects should be similarly addressed by the multidisciplinary team, including psychologists, to improve quality of life and patient satisfaction.

Many of the VMs cannot be cured but can only be controlled. It is important to convey full understanding of this concept, when counseling patients and their families at the onset of diagnosis in order to set appropriate levels of expectation from treatment. Frequently multiple treatments are required to control vascular anomalies, which may require lifelong medical and psychological care.

Classification

Vascular anomalies are divided into vascular tumors, of which infantile hemangiomas (IHs) are by far the most common type, and VMs. The natural history of these two groups is quite different. These lesions are also fundamentally distinct in their radiographic and histologic appearances as well as their biologic behavior and prognosis. All vascular anomalies are best classified using the scheme introduced by Muliken and Glowaki and recently codified by the International Society for the Study of Vascular Anomalies. In the past, VMs were erroneously called hemangiomas, which led to fundamental errors in management and patient outcomes.

IHs are vascular tumors composed of rapidly dividing hematogenous endothelial cells. These lesions will be noticed during the first few months of life and can grow rapidly until about 1 year of age. At this age, IHs begin to regress or involute. Over several years, many IHs will eventually disappear but may leave evidence, or sequelae, of their early presence. True IHs are histologically similar to placenta and may be the result of early stem cell progenitors from this tissue. The clinical similarities between IHs and placenta in their growth patterns are convincing. Placenta will grow for 9 months and involute when a baby is born—IHs grow for about 1 year and then begin to involute and eventually disappear.

VMs are anomalous vascular channels lined by a single endothelium that are usually present at birth. VMs are classified based upon their blood vessel type and can be seen early in life. Depending on the depth of the VMs, they may not appear obvious until later in life. They do not involute and will continue to slowly grow with ultimately destructive and life-threatening consequences. This distinction between IH and VM is extremely important to understand. Later in this chapter, the criteria for diagnosis of each type of vascular malformation will be addressed. **Table** 37.1 lists the classification of vascular anomalies.

Table 37.1 ISSVA Classification of Vascular Anomalies

Vascular Anomalies				
Vascular Tumors			Vascular Malformations	
Benign	**Locally Aggressive**	**Malignant**	**Simple**	**Combined**
Infantile hemangioma	Kaposiform hemangioendothelioma	Angiosarcoma	Capillary malformation (C)	CVM and CLM
Congenital hemangioma	Retiform hemangioendothelioma	Epithelioid hemangioendothelioma	Lymphatic malformation (LM)	LVM and CLVM
Tufted hemangioma	PILA and Dabska tumor		Venous malformation (VM)	CAVM
Spindle cell hemangioma	Composite hemangioendothelioma		Arteriovenous malformation (AVM)	CLAVM
Epithelioid hemangioma	Kaposi sarcoma		Arteriovenous fistula	
Pyogenic granuloma				

Abbreviated ISSVA classification for Vascular Anomalies by International Society for the Study of Vascular Anomalies is licensed under a Creative Commons Attribution 4.0 International License.

HEMANGIOMAS

IHs are composed of proliferating immature endothelial cells that express histologic markers found on placental blood vessels as reported by North et al.[1] These are the most common tumor of infancy and are present in ~5% of the population. They occur more frequently in infants from mothers with early trimester bleeding, preeclampsia, and placental anomalies.[2] IHs are rarely noted at birth, but commonly a macular erythema area of the skin is noted in the first 6 weeks of life and then a rapid growth is usually noted. These lesions present in the head and neck region in over 60% of cases. Most IHs grow within the first 3 months of life and continue to grow up to 1 year of age and may be very extensive. After 1 year of age, IHs will go into a quiescent phase and began to involute and eventually resolve. Most will involute completely by 7 years of age. This natural history is important to differentiate IHs from other congenital vascular lesions and will help to guide management decisions.

IHs can present as focal or segmental lesions involving multiple areas. They are also characterized as superficial, deep, or compound. It is rare for a focal IH to involve muscle or penetrate beyond subcutaneous fat. However, an IH involving the parotid gland can involve the gland itself.

When IHs involve the lip, eyelids, orbit, and nose, or subglottic region, they may lead to significant functional and/or aesthetic problems during the

rapid proliferation phase (**Fig.** 37.1A–C).

Figure 37.1. A: Ulcerative hemangioma of the lower lip. **B:** Paranasal hemangioma. **C:** Segmental hemangioma involving the temple area and the orbit causing visual obstruction.

Infants with five or more focal IHs may also have hepatic involvement and should undergo abdominal ultrasound. Segmental IHs are usually more complex and in the head and neck will follow a trigeminal nerve distribution. They are diffuse and compound and maintain irregular borders. It is common to see more than one facial subunit involved (**Fig.** 37.2). They commonly penetrate into deep fascial planes of the head and neck. IHs involving the beard distribution are those most commonly described. These usually involve the lower lip, chin, neck, and preauricular areas, and ulcerations are frequently present. As many as 60% of IHs with a segmental beard distribution will involve the subglottis and require airway endoscopy.[3] Patients with segmentally distributed IHs should be evaluated for PHACES syndrome (posterior fossa malformations, hemangiomas, arterial lesions, cardiac abnormalities, eye abnormalities, and sternal clefts).

Figure 37.2. Right facial segmental hemangioma in child with PHACES.

The diagnosis of IHs is primarily clinical. They are not usually noticed at birth, and when the child is between 1 and 3 months old, these lesions will begin growing and after 1 year, they will begin to involute. Biopsies are not usually necessary and scans are not usually indicated unless there is a concern for the PHACES syndrome.

The management of IHs has improved significantly in recent years. Because of their natural involution, IHs were historically managed with observation only. Even though they resolve spontaneously, they can cause significant functional and disfiguring sequelae. Most problematic events from IHs will occur during the proliferative phase and may include ulceration, bleeding, pain, disturbance of vision, airway compromise, and feeding

difficulties. The late sequelae will include scarring, telangiectasias, and fibrofatty residuum.

The treatment of IHs may involve surgical excision, laser therapy, topical therapy, intralesional corticosteroids, systemic corticosteroids, systemic β-blockers, and vincristine chemotherapy. If an infant has a focal hemangioma, which is primarily deep, the lesion can typically be observed unless ulceration or bleeding occurs. For the superficial focal lesions, laser therapy or surgery can be used to control the IH. For the problematic hemangiomas, β-blockers have been found to be effective in over 95% of the cases with rapid involution. The most common dose of β-blockers has been 2 mg/kg/day in divided doses two to three times daily.[4] During the involution phase, surgical excision can give excellent results and prevent late sequelae.

VASCULAR MALFORMATIONS

As mentioned previously, VMs are very different from IHs. They do not involute and will continue to progress throughout life. They may have rapid growth spurts at different times of life. Our research has shown that many VMs have progesterone receptors[5] and this is associated with growth spurts during puberty, use of oral contraceptives, and pregnancy. We commonly see patients who did not notice their malformation until these events occurred. There are also unknown causes for growth spurts, which have not been identified yet. The destructive and life-threatening events that occur from many VMs will be illustrated.

Capillary/Venular Malformations

Capillary/venular malformations (CM) are histologically composed of congenital ectasia of thin-walled, small-caliber capillaries and veins of the skin. The simplest presentation of a capillary malformation is known as a nevus flammeus or “port-wine stain” (PWS). They occur in 0.3% of newborns and are visible at birth. They commonly appear as sharply demarcated, homogeneous, erythematous macules, typically located on the face or neck. They can also involve the mucosa of the upper aerodigestive track when the overlying skin is involved, such as the lip and cheek areas. If left untreated, CMs will darken in color and develop nodular changes. Hyperplasia of the underlying soft tissues commonly occurs (**Fig.** 37.3).

Figure 37.3. Capillary malformation (PWS) of the right face with tissue hypertrophy.

Capillary malformations usually occur spontaneously within a population and are the most common cutaneous vascular malformation seen. There is not an identifiable genetic component, although a subclass of CMs associated with arteriovenous malformations (AVMs) has been identified as having autosomal dominant transmission and associated mutations in the RASA1 gene.[6]

Approximately 75% of capillary malformations are located in the head and neck. Extracutaneous involvement can also occur and affect the central nervous system, eyes, or other organs.

Capillary malformations may be an isolated cutaneous lesion or a syndrome-related lesion. Parkes-Weber syndrome presents as a cutaneous

capillary malformation with hypertrophy of limbs and can have arteriovenous fistulas and congenital varicose veins.[7] Klippel-Trenaunay syndrome (KTS) is associated with three distinct features: the presence of a PWS, soft tissue or bony hypertrophy (or both) of the extremities, and varicose veins or venous malformations. Diagnosis is confirmed by the presence of any two of the three features.[8]

The treatment for capillary malformations is primarily performed using lasers. If left untreated, the affected area of skin darkens and hypertrophies to cause thick and nodular lesions that lead to disfigurement and often subsequent psychological disturbance. The pulsed-dye laser (PDL) has been the most commonly used laser for cutaneous involvement of PWSs. It commonly requires multiple, frequent treatments and may lighten and maintain a sustained response for several years after PDL therapy. The intense pulsed light (IPL) laser is also shown to be effective for PWSs.

Only about 10% of patients with PWS can be cured with laser therapy, and these are usually those individuals with small superficial lesions. Treatment during infancy can lighten the PWS after an average of three or four sessions.[9] It is rare to see skin complications from these two lasers.

Older patients with very thick and nodular PWSs may require surgery to remove the most disfiguring and symptomatic lesions (**Fig.** 37.4).

Figure 37.4. Two older patients with typical untreated capillary malformations with color changes, hypertrophy, and cobblestone appearance.

Lymphatic Malformations

Lymphatic malformations (LMs) can be classified as macrocystic, microcystic, or mixed. The old terminology, cystic hygromas and lymphangiomas, is no longer recommended. Large macrocystic LMs can present during early infancy and are frequently life threatening.[10] They can be very large and obstruct the airway or involve the chest as well. They require emergent treatment (**Fig.** 37.5).

Figure 37.5. Extensive macrocystic LM or the neck and chest in a newborn causing airway obstruction.

The diagnosis of LMs is usually not difficult. The history can vary, but they commonly enlarge during childhood or during puberty. They can be cystic and translucent, and they are not typically compressible like venous malformations. When the mucosa or skin is involved, vesicles are visible and obvious. Vesicles are pathognomonic of LMs, especially the microcystic forms. The vesicles are usually clear but may have blood in the vesicles because of local trauma. The appearance of the vesicles has been compared to “fish eggs” or caviar (**Fig.** 37.6).

Figure 37.6. Vesicles seen only with lymphatic malformations. The blood in the vesicles reflects local trauma.

LMs may be isolated lesions, but more commonly, they involve multiple sites, such as the face, tongue, mandible, larynx, and neck.[10] The bones of the face or mandible involved with LM usually hypertrophy causing bony distortion of the face. Also, it is not uncommon for LMs to have a component of venous malformations.

The most serious potential complication of LM is airway obstruction, which may be caused by an enlarged tongue filled with an LM or a large lesion of the neck causing compression of the trachea, larynx, and/or pharynx. When the tongue is involved, it is usually microcystic and diffusely enlarged and can fill the entire oral cavity and protrude out of the mouth (**Fig.** 37.7A and B). Most macrocystic LMs are found in the neck and usually

consist of multiple large cysts and commonly cause airway obstruction.

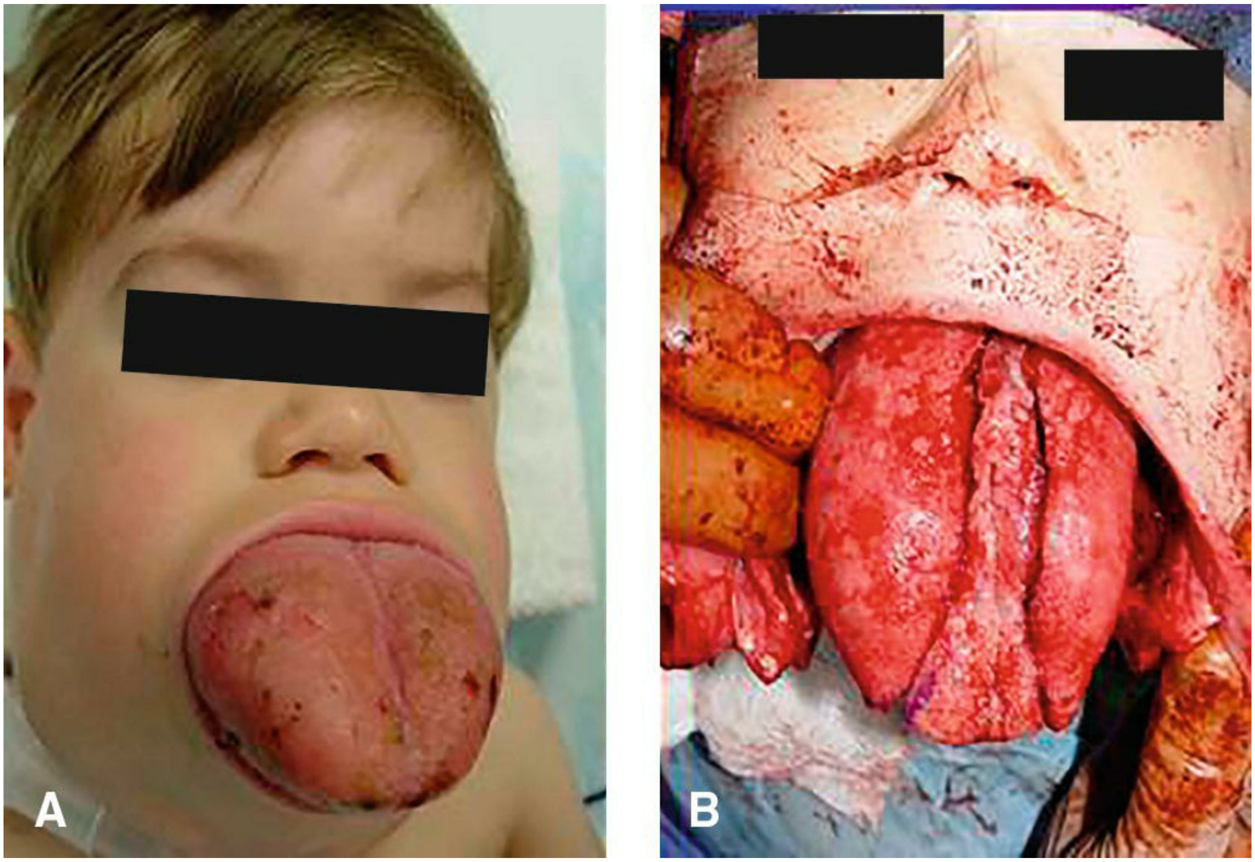

Figure 37.7. A: Extensive microcystic LM of the tongue. **B:** Surgical reduction of tongue.

With regard to imaging, the MRIs with T2-weighted images are the most useful images, as the LM will appear as hyperintense areas on these images. They can appear similar to venous malformations on these scans, but the physical examination can differentiate the two lesions. Also, on the MRI, the LM frequently will have "fluid–fluid" levels, which represent two different fluid densities and are diagnostic. CT scans or angiograms are not particularly helpful and should not be ordered if the diagnosis of LM is highly suspected.

Management of LMs commonly depends upon the expertise of the treating physician or team.[11] During infancy, the baby may present with a huge mass in the neck causing airway distress. A tracheotomy may be necessary to ensure the airway. If there is no urgency, sclerotherapy can be attempted and can be successful. There are various sclerosing agents that can

be used. Outside of the United States, it is common to use OK-432, which is a streptococcus toxin, but it is not approved by the FDA in the United States except on clinical trials. We have used alcohol and doxycycline, and more recently, we are using bleomycin in low doses. If there is an urgency to treat the large cystic LMs, surgery by an experienced surgeon should be considered. It is important for the surgeon to realize that a suction drain is important and must be left in place for a prolonged period of 2 to 4 weeks. Also, antibiotics and steroids are important for several weeks after surgery. If there are only limited macrocystic LM lesions, in the neck, it may be possible to cure the LM.

With the LMs that involve the tongue and face, surgery has been very useful, but the facial nerve is at significant risk. In the past, sclerotherapy has not been effective for microcystic LM, but in the past few years, bleomycin has been found to be effective in treating lingual LM. It is injected directly into the tongue and can shrink the lesions and the tongue. Often multiple sclerotherapy treatment sessions are necessary to obtain significant shrinkage. Although this approach does not cure the LM, it can control these lesions for many years.

A total or subtotal resection of the tongue should be avoided because it can result in severe permanent functional disabilities with inability to speak or swallow. Also, without the mass of the tongue, the mandible tends to collapse medially resulting in loss of the space where the tongue normally is located. This in turn can lead to major mandibular hypertrophy and severe malocclusion requiring major surgical reconstruction and orthodontics (**Fig.** 37.8). Also, dental caries are common and may require dental rehabilitation or extraction.

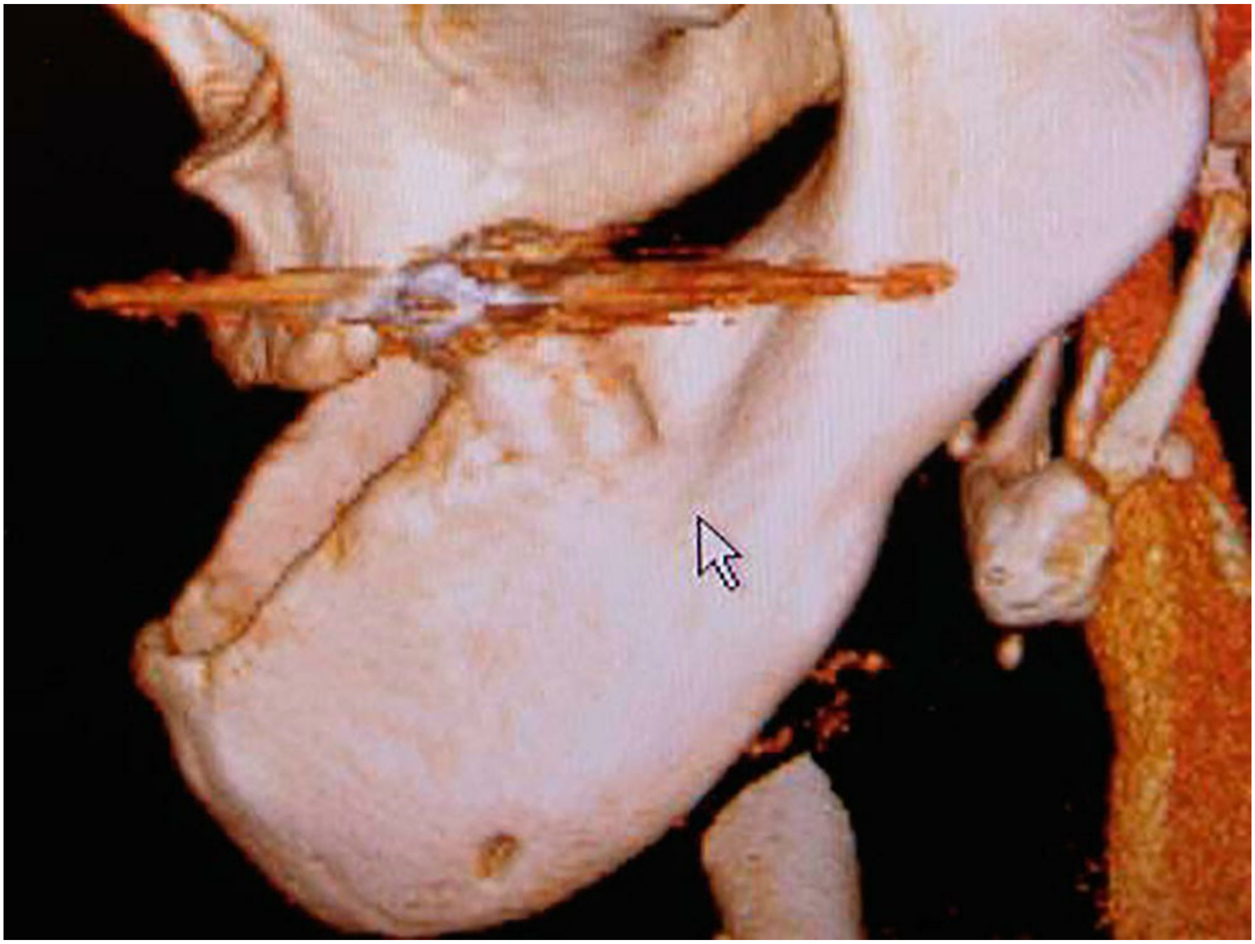

Figure 37.8. Hypertrophy of the mandible with extensive LM of the tongue and face.

Lasers can also be helpful in the treatment of LM. The carbon dioxide (CO_2) laser is the primary laser used and it is used to vaporize the superficial lesions and vesicles down to the submucosal tissues, such as those on the tongue.[10] Large mucosal lesions on the palate or larynx can be lasered down to normal underlying tissue. An Nd:YAG laser can be helpful with the deeper component of the LM.

Venous Malformations

Venous malformations are usually present at birth but may not be noticed until later in life. They consist of abnormal veins and may be small and isolated or can be multifocal and very extensive. The diagnosis is usually very easy to make, as these lesions will typically have a bluish discoloration when near a surface, such as skin or mucosa[12] (**Fig.** 37.9). In addition, they

are compressible and will refill when pressure is released. Another distinguishing characteristic of venous malformations is that when the area involved is in a dependent position, the venous malformation will enlarge or engorge and when elevated, the engorgement will decrease.

Figure 37.9. A–D: Examples of head and neck venous malformations involving skin and mucosa.

It is very common to have pain associated with venous malformations, especially around the eye and temple area, and this pain may be quite severe even requiring narcotics for control. The tongue, oropharynx, and hypopharynx can be involved, and when this occurs, it can lead to airway obstruction, especially when reclining in a supine position. Furthermore,

when the mucosal surface is involved, bleeding may occur which may be life threatening.

The best imaging study for venous malformations is an MRI with T2-weighted images, which will demonstrate the malformation as hyperintense areas (**Fig.** 37.10). Phleboliths can commonly be seen within the hyperintense area as circular flow voids. These represent calcified blood clots. On a CT scan, the phleboliths will show up as calcifications. LMs will also be hyperintense on the MRI, but the physical examination can usually differentiate between an LM and venous malformation.

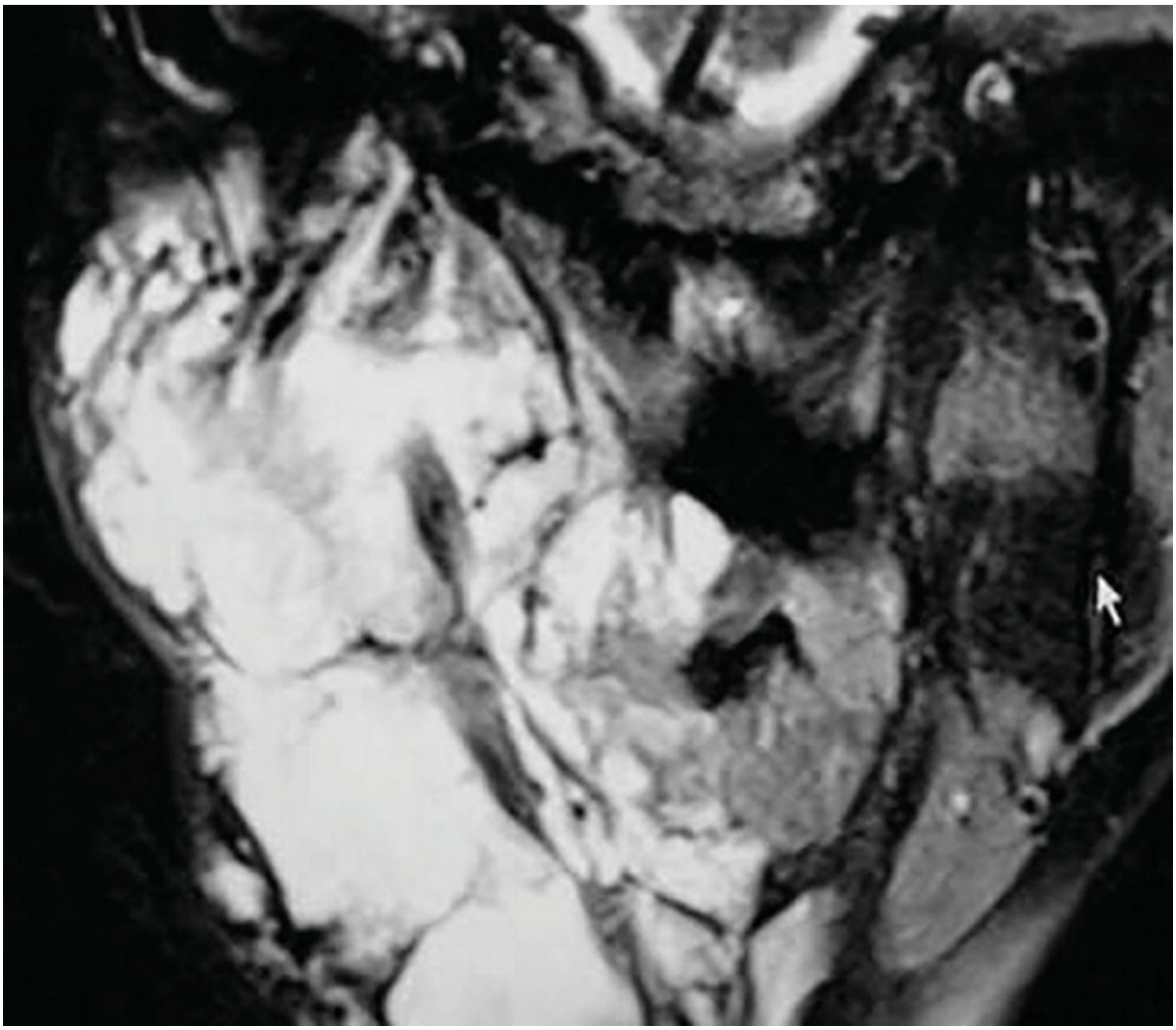

Figure 37.10. MRI of venous malformation demonstrating extensive involvement of the neck and tongue. This is a T2-weighted image showing the VM as hyperintense.

An arteriogram or MRA will not demonstrate a venous malformation because there are usually no arterial feeders. Therefore, these imaging studies are not recommended in the evaluation of suspected venous malformations.

With regard to management, the small, superficial, isolated lesions can be treated with surgery or using an ND:YAG laser. We do not recommend alcohol sclerotherapy on superficial lesions because of the potential for sloughing of the overlying skin or mucosa.

The multifocal, larger venous malformations are much more difficult to treat.[12] If there are lesions that appear circumscribed with definitive margins, they can usually be resected adequately (**Fig.** 37.11). If they intimately involve the skin or mucosa, those areas should be removed with the lesions.

Figure 37.11. A large venous malformation of the neck, which had distinct borders on MRI indicating possible role for resection.

Most of the larger, multifocal venous malformations are best treated with sclerotherapy, primarily using alcohol.[13] In the past few years, bleomycin has become more popular for sclerotherapy and can be very effective.[14] It can be used when skin or mucosa is involved without much risk of sloughing. Since bleomycin is a chemotherapy agent, it is best to give small doses each treatment and the total amount monitored to avoid risk of pulmonary fibrosis, which can occur when over 200 units total dose have been given. When bleomycin is used, we use only about 6 to 15 units at a time. We dilute a 15-unit vial of bleomycin with 7 mL of 2% lidocaine and 1 mL of Decadron, or it can be mixed with albumin and air to make foam, which can stay in the VM longer. The bleomycin or alcohol can destroy the endothelium of the venous malformations causing blood clots, and as the blood clots shrink, the malformations shrink with it. However, the adjacent areas, which are untreated, will continue to expand with time.

It is rare for one sclerotherapy treatment to destroy multifocal venous malformations. It is also common for patients to undergo multiple sclerotherapy treatments. Many of these large, multifocal venous malformations cannot be cured but can be well controlled with proper treatment. It is important to inform the patients and their families that the goal is to control the disease rather than cure it, so that they understand repeated treatments are necessary and that follow-up care throughout life is important.

When mucosa is involved and the VM is superficial and bluish, it is best to use an Nd:YAG laser with a power setting of 15 to 25 watts and duration of 0.5 to 1.0 seconds exposure time. Shrinkage of the VM occurs immediately and leaves a white spot. A polka-dot pattern is important because if the treated spots are too close and overlapping, sloughing of the mucosa and bleeding may occur. In the pharynx, the laser treatment should begin distally and progress proximally. This can be repeated every 2 months or more. The laser treatment will shrink the VM and also thicken the mucosa so that bleeding later is unlikely.

Arteriovenous Malformations

AVMs are congenital vascular anomalies where there is an aberration of the capillary bed and the arterial blood flow shunts through the bed into the venous system almost directly. This abnormal capillary bed is called a nidus. The arterial feeder vessels and the draining veins will get very large because

of this rapid flow of blood. The nidus will also get larger because of hemodynamic changes. An AV fistula usually has only one or two arteries, which shunt into the adjacent vein(s), whereas an AV malformation has multiple arteries and veins involved. The following discussion involves extracranial AVMs.

AVMs appear to be heterogenous. There are some AVMs that have a distinct history of trauma to the site involved and probably are AV fistulas that can become identical to AVMs when left untreated. There are others that are more focal and seem to expand through hemodynamic factors. Then, there is a group of AVM that are very aggressive and seem to expand through invasion and destruction of adjacent tissue.

As mentioned in the introduction, some AVMs have many similarities to low-grade malignancies, and we feel they should be treated as such. Our philosophy is to treat AVMs as early as possible and to be aggressive. This may be the only chance for cure. Because many AVMs involve the face, eyes, ears, nose, and tongue, the treating team must weigh the consequences of treatment versus the natural history of the AVM. AVMs are very destructive, and we have shown in our research that they have both clinical and molecular characteristics of low-grade malignancies. It is important to understand the natural history of AVMs in order to decide on the most appropriate treatment.[15]

Many AVMs cannot be cured but can be controlled with proper treatment. The treating team, the patients, and their families should be aware of this and counseled properly.

AVMs may be focal or multifocal. The focal AVMs have a better chance for cure and should be treated as early as possible. We disagree with the philosophy that AVMs should not be treated until they become symptomatic because they may be incurable at that time.

We have seen AVMs that had a definite history of trauma to the involved area and feel that these AVMs may have started as AV fistulas and, left untreated, become AVMs. These entities usually involve more superficial areas, such as the lip, nose, eyelids, or ear. There is a much better chance for cure with this type of AVM.

Multifocal AVMs are much more difficult to treat and cure. All of the sites involved may not be obvious initially. Also, it is common to think that

an AVM is cured with surgery or embolizations and to find a few weeks or months later that the AVM is growing with a vengeance. We have patients whose recurrences were not identified until 10 years later. We rarely tell a patient that we feel his or her AVM is cured.

The diagnosis of an AVM is not always easy. It is based on the history, physical examination, and special radiologic studies.[16] An AVM can occur at any age. However, it is rare to see an AVM in an infant, but when it occurs, these lesions are usually very aggressive. It is more common to see an AVM present when a child is undergoing puberty, around 10 to 13 years of age. The AVM has been there since birth but is being stimulated to grow related to hormone receptors. They will expand rapidly during this phase unless treated. Also, it is common to see an AVM recognized during pregnancy or when oral contraception is used. It is less common to see an AVM present after the age of 30, but it can occur. We feel that many of these that occur later in life are probably related to trauma and were AV fistulas that progressed to AV malformations.

A common history for an AVM is that the patient or parent will notice a red blush in the skin and that the tissues underneath that area are enlarging. They may or may not have noticed a pulsation in that area, and bleeding can occur if the area begins to ulcerate when involving the skin or the mucosa of the nose or mouth. It is quite common for patients to be told that they have a hemangioma and that it will go away with time.

On the physical examination, an AVM often appears as an erythematous area, which may have small varicosities in the skin or mucosa, and can resemble a PWS. Early in the disease process, the area involved may just look enlarged. In addition, AVMs can cause hypertrophy of the soft tissues it involves and the adjacent bones because of the rich blood supply (**Fig.** 37.12). Pulsation may or may not be palpable, and there is usually no thrill or bruit in the early stages. As the AVM enlarges, pulsation is more noticeable by the patient and the overlying skin or mucosa ulcerate and bleed intermittently. Bleeding is usually bright red and may be profuse and difficult to control. If the mandible or gum tissue is involved, it is common for bleeding to occur while brushing the teeth.

Figure 37.12. A 23-year-old male with an AVM of the face with hypertrophy of the tissues and varicosities of the overlying skin.

With regard to imaging studies, an arteriogram is the most definitive test. A CT arteriogram (CTA) (**Fig.** 37.13) or an MR arteriogram is very helpful to diagnose and delineate the extent of an AVM as well as its feeding vessels. The three-dimensional views of a CTA can be very helpful, especially with superficial lesions (**Fig.** 37.14). We prefer a CTA because it can be done quickly and is less expensive than an MRA. Arteriography is usually not performed unless the treatment plan includes using embolization followed by surgery, in which case embolization should be performed 1 to 3 days prior to the planned surgical procedure.

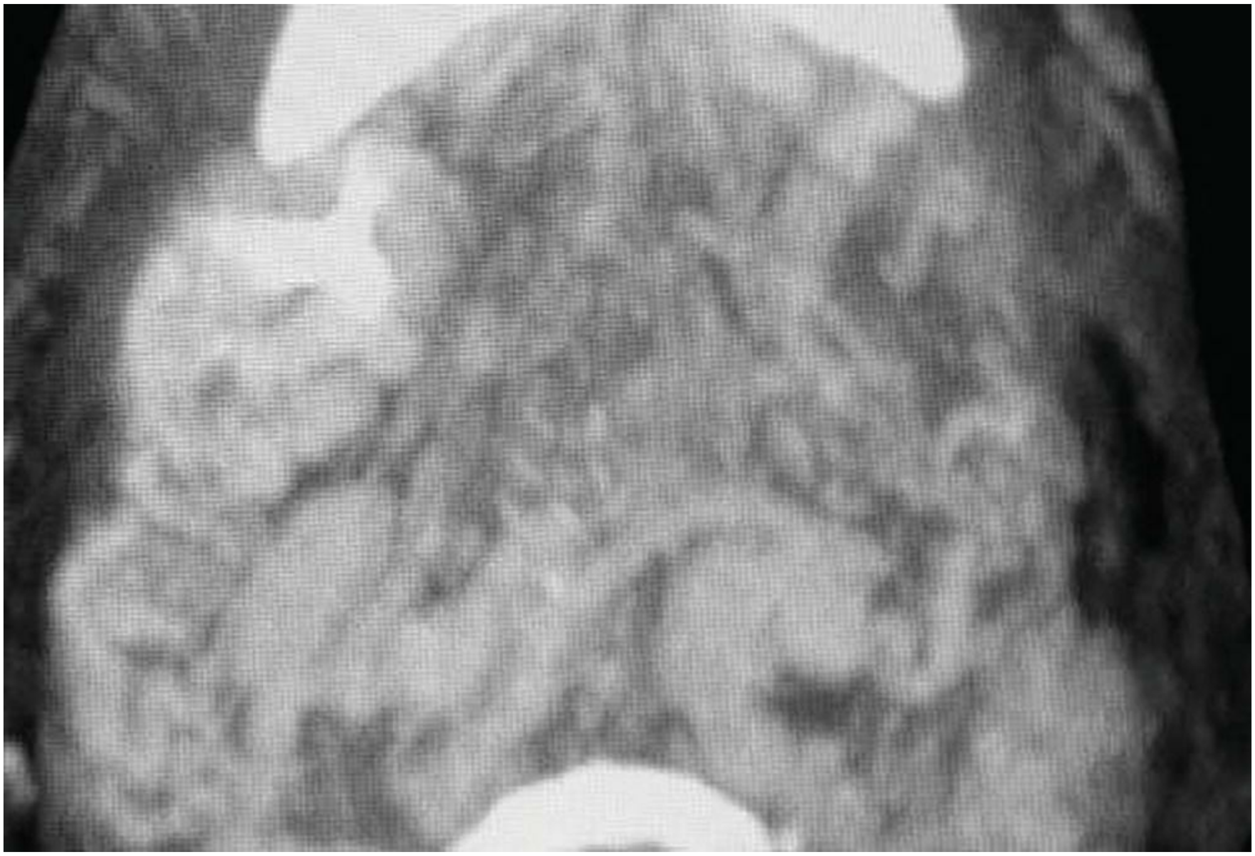

Figure 37.13. CTA illustrating the numerous huge vessels in an AVM of the tongue.


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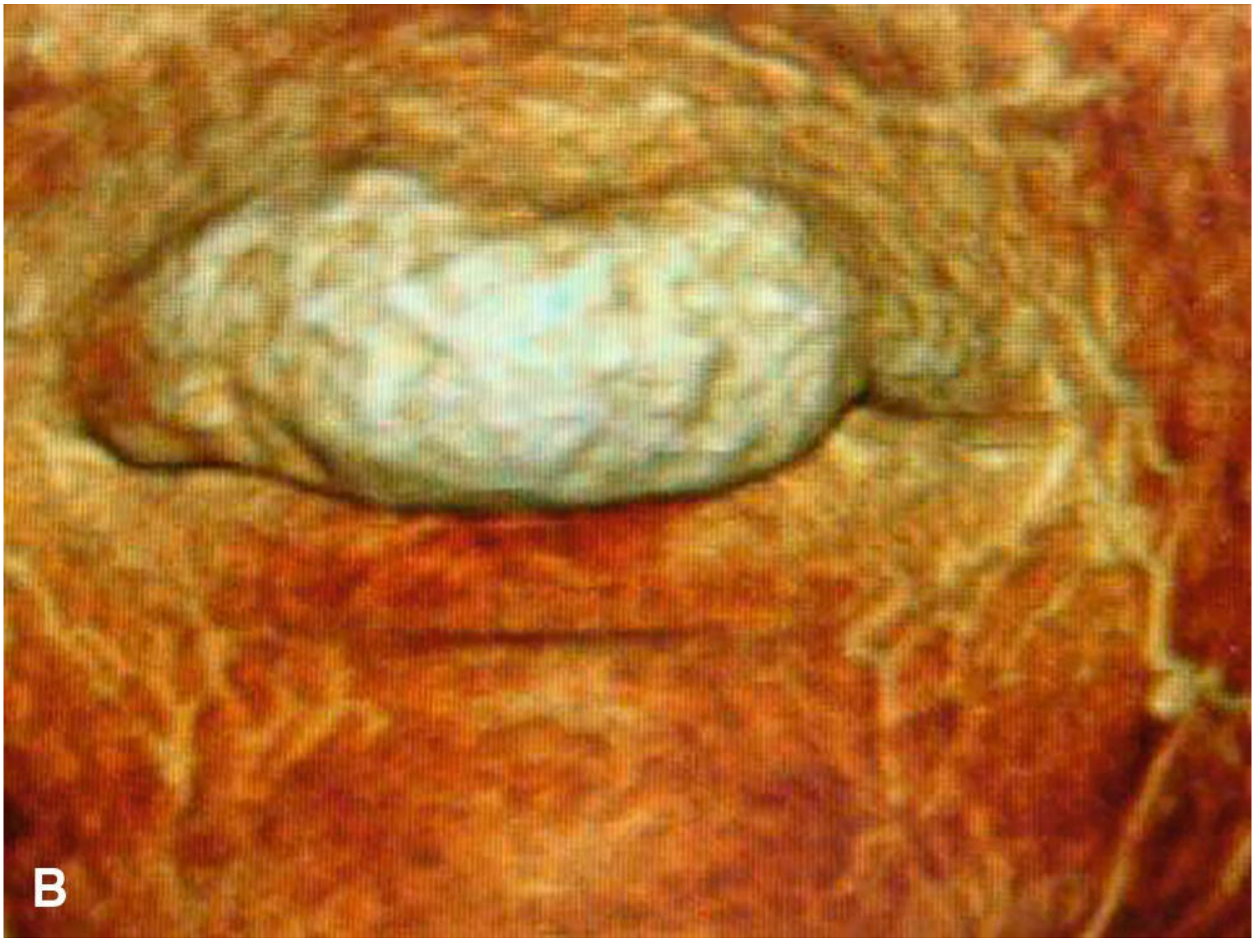

Figure 37.14. A and B: CTA with 3D reconstruction views of an AVM of the lip in two different patients.

An arteriogram of an AVM demonstrates a vascular blush, which is the nidus, with the feeder arterial vessels and early venous outflow tracts. When evaluating an arteriogram for the extent of an AVM, one must be very careful in the interpretation, because some, or a lot of the nidus, may be hidden. Understanding the flow dynamics is crucial. The largest arteries may shunt most of the contrast dye into one nidus, and there may be other multifocal areas fed by smaller vessels that may not reveal themselves. During embolization when the embolic material blocks off a nidus and more contrast is injected, other parts of the nidus may become evident, which explains why the extent of many AVMs may be underestimated.

Treatment for extracranial AV malformations can be very complex and should be performed by experienced teams who specialize in vascular anomalies.[16] A team approach is very important. A surgeon without other

team support will most often offer surgery as the primary treatment modality, and an interventional radiologist, practicing without other specialists, may choose embolization alone as the primary treatment modality. A pediatrician, dermatologist, or plastic surgeon who does not treat VMs may recommend watching and waiting, because "they may go away with time." To make a proper decision, all specialties should be involved in treatment selection and planning.

We have classified AVMs as focal or multifocal. The focal AVMs are most often localized and the extent of involvement can usually be determined. We feel that the majority of focal AVMs can be treated surgically and if adequately resected can be cured (**Fig.** 37.15). Embolization can be used, but, in our experience, is often associated with recurrence. Furthermore, when the focal AVMs involve the overlying skin or mucosa, embolization, even with small amounts of embolic material, can cause significant sloughing of tissue (**Fig.** 37.16).

Figure 37.15. A and B: Focal AVM of the lip treated with surgical resection.

Figure 37.16. AVM of lip treated with only 1 mL alcohol resulting in sloughing of the lips.

Multifocal AVMs are the biggest challenge and rarely can be cured. The primary treatment modalities have been embolization and surgery, but as described below, pharmacotherapy with doxycycline or propranolol may be useful and play a larger role in the future.

Embolization of AVMs is now the treatment utilized most commonly.[16] One major reason is that there are very few surgeons who are capable and willing to operate on AVMs. Embolization is usually performed through an arteriogram but can also be performed through a direct puncture technique. This technique should be performed by an experienced interventional radiologist. The most common embolic material used is alcohol, but also, glue and onyx are commonly used. When mucosa or skin is involved, alcohol and glue can cause sloughing of the tissues. It would be rare for one embolization procedure to destroy or cure an AVM. It is not uncommon for

patients to undergo 10 or more embolization procedures over time with persistence of the AVM (**Fig.** 37.17). Embolization can also be performed as a preoperative procedure.[17] If this is the situation, we recommend that surgery be performed within 1 to 3 days, because revascularization occurs.

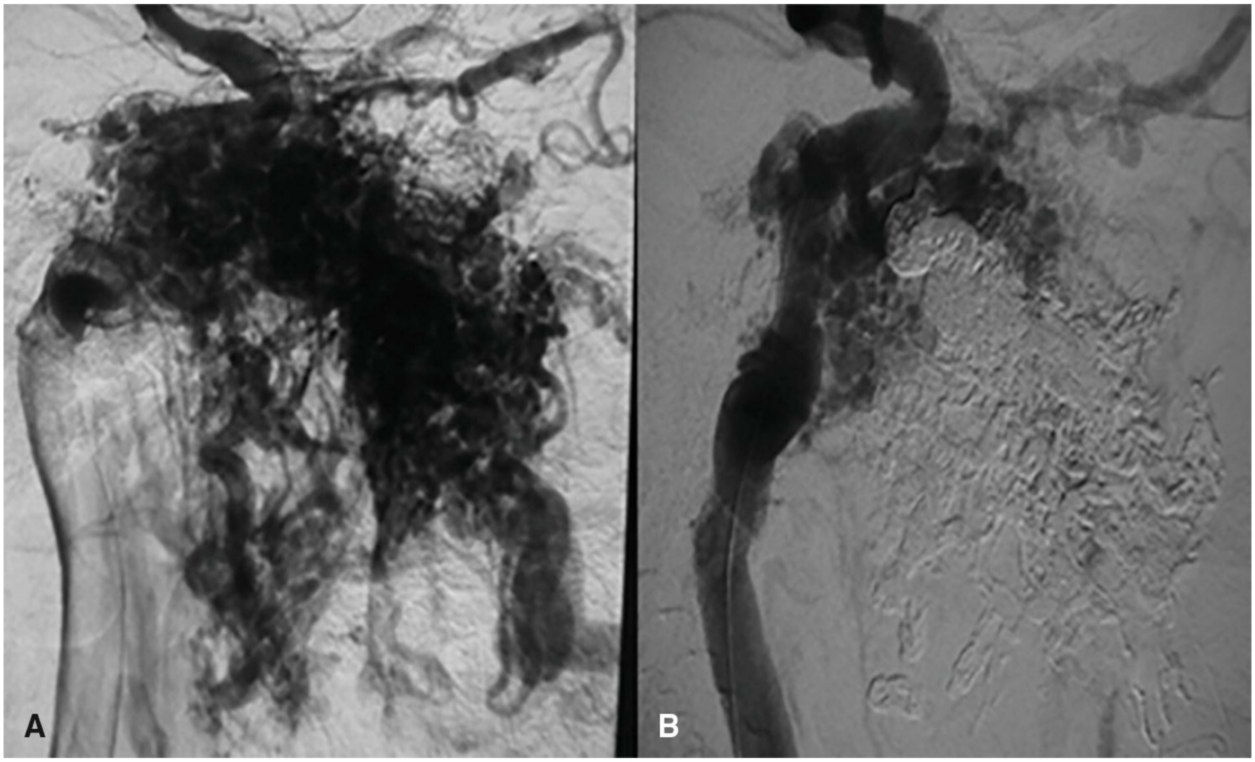

Figure 18.10. A: Contrast dye in AVM deep in the face fed by branches of the internal carotid artery. **B:** Onyx can be seen in the AVM after embolization.

We have monitored patients who have embolization procedures for large AVMs and require multiple treatments, and we have found that there is significant radiation exposure during the procedures. We have found that a patient can have as much as 600 cGy of radiation exposure during one prolonged treatment. This can cause cataracts, skin or other cancers, and poor healing if they undergo surgery. Patients and their families should be aware that this may occur. It is necessary to use embolizations for AVMs because of the major tissue destruction and potential for death if these lesions are not controlled.

Surgery may be the best choice when the AVMs are very extensive and embolization procedures have failed. Major bleeding is a concern and should

not be underestimated. Partial resection is not usually helpful and may result in more rapid growth of the residual AVM. An experienced head and neck surgeon should perform surgical resection (**Fig.** 37.18). We try to preserve the facial nerve during surgery, and if preserved, facial function may return 6 to 12 months later. However, the patient will have a facial nerve paralysis due to the difficulty in dissection, but alternatively, if the AVM is not properly resected, it may destroy the entire face. When the orbit is involved, exenteration of the orbit may be necessary (**Fig.** 37.19). For extensive surgical resections, reconstruction with microvascular free flaps may be required.

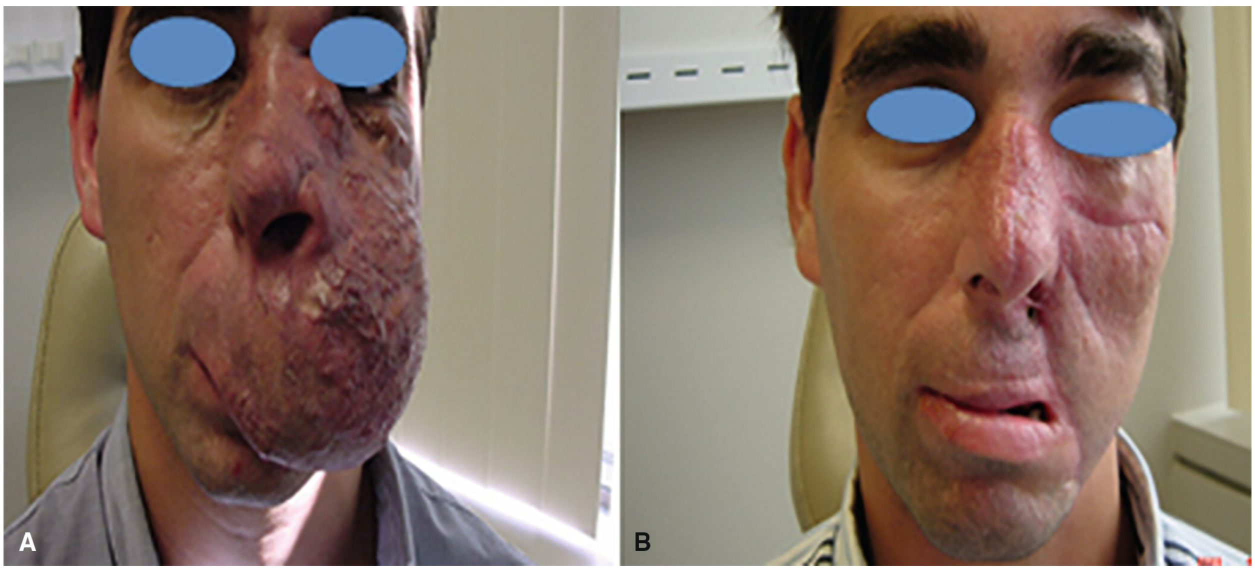

Figure 37.18. A and B: Preoperative and postoperative views of patient with extensive AVM of face and palate.

Figure 37.19. A and B: Extensive, destructive AVM of the face and orbit, before and after resection with free flap reconstruction.

Lasers have very little role in treating AVMs. We have had some success using an Nd:YAG using both gentle superficial and interstitial techniques, but success with this approach requires significant experience using this modality.

We have treated a number of AVM patients with different medications targeting their underlying biology and have seen some favorable responses. Evaluation of AVMs for expression of MMP-9 (matrix metalloproteinase) by our group has revealed significant expression of this enzyme in AVMs. Based on this, we have hypothesized that the enzyme may increase tissue breakdown allowing for expansion of the vessels and have proposed the use of doxycycline, a nonspecific inhibitor of MMP for the treatment of AVMs. In our experience treating patients with AVMs with doxycycline (100 mg BID), 50% state that they have decreased symptoms, such as less bleeding, indicating that it can stabilize AVMs in certain cases.

Based on the success in using propranolol in treating IH, we have tested its use in treating patients with AVMs and found that between 25% and 50% of the patients notice decreased pressure and bleeding. We feel that propranolol may decrease the blood pressure and heart rate, which can decrease flow pressures in the nidus of an AVM in some patients. The dosage of propranolol is 1 to 2 mg/kg/day depending on the patient's tolerance for

the medication.

Based on our research showing that there are biologic and clinical similarities of AVMs to low-grade cancers, we feel that pharmacotherapy may be the answer to finding a cure for some AVMs. This is ongoing research on our Department.

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